Novel Peptides as NS3-Serine Protease Inhibitors of Hepatitis C Virus

Field of Invention

The present invention relates to novel hepatitis C virus ("HCV") protease inhibitors, pharmaceutical compositions containing one or more such inhibitors, methods of preparing such inhibitors and methods of using such inhibitors to treat hepatitis C and related disorders. This invention specifically discloses novel peptide compounds as inhibitors of the HCV NS3/NS4a serine protease. Priority for the invention is based on U.S. patent applications Serial Number 60/220,108 filed July 21, 2000, and Serial Number 09/908,955 filed July 19, 2001.

Background of the Invention

Hepatitis C virus (HCV) is a (+)-sense single-stranded RNA virus that has been implicated as the major causative agent in non-A, non-B hepatitis (NANBH), particularly in blood-associated NANBH (BB-NANBH)(see, International Patent Application Publication No. WO 89/04669 and European Patent Application Publication No. EP 381 216). NANBH is to be distinguished from other types of viral-induced liver disease, such as hepatitis A virus (HAV), hepatitis B virus (HBV), delta hepatitis virus (HDV), cytomegalovirus (CMV) and Epstein-Barr virus (EBV), as well as from other forms of liver disease such as alcoholism and primary biliar cirrhosis.

Recently, an HCV protease necessary for polypeptide processing and viral replication has been identified, cloned and expressed; (see, e.g., U.S. Patent No. 5,712,145). This approximately 3000 amino acid polyprotein contains, from the amino terminus to the carboxy terminus, a nucleocapsid protein (C), envelope proteins (E1 and E2) and several non-structural proteins (NS1, 2, 3, 4a, 5a and 5b). NS3 is an approximately 68 kda protein, encoded by approximately 1893 nucleotides of the HCV genome, and has two distinct domains: (a) a serine

protease domain consisting of approximately 200 of the N-terminal amino acids; and (b) an RNA-dependent ATPase domain at the C-terminus of the protein. The NS3 protease is considered a member of the chymotrypsin family because of similarities in protein sequence, overall three-dimensional structure and mechanism of catalysis. Other chymotrypsin-like enzymes are elastase, factor Xa, thrombin, trypsin, plasmin, urokinase, tPA and PSA. The HCV NS3 serine protease is responsible for proteolysis of the polypeptide (polyprotein) at the NS3/NS4a, NS4a/NS4b, NS4b/NS5a and NS5a/NS5b junctions and is thus responsible for generating four viral proteins during viral replication. This has made the HCV NS3 serine protease an attractive target for antiviral chemotherapy.

It has been determined that the NS4a protein, an approximately 6 kda polypeptide, is a co-factor for the serine protease activity of NS3. Autocleavage of the NS3/NS4a junction by the NS3/NS4a serine protease occurs intramolecularly (i.e., *cis*) while the other cleavage sites are processed intermolecularly (i.e., *trans*).

Analysis of the natural cleavage sites for HCV protease revealed the presence of cysteine at P1 and serine at P1' and that these residues are strictly conserved in the NS4a/NS4b, NS4b/NS5a and NS5a/NS5b junctions. The NS3/NS4a junction contains a threonine at P1 and a serine at P1'. The Cys→Thr substitution at NS3/NS4a is postulated to account for the requirement of *cis* rather than *trans* processing at this junction. See, e.g., Pizzi et al. (1994) Proc. Natl. Acad. Sci (USA) 91:888-892, Failla et al. (1996) Folding & Design 1:35-42. The NS3/NS4a cleavage site is also more tolerant of mutagenesis than the other sites. See, e.g., Kollykhalov et al. (1994) J. Virol. 68:7525-7533. It has also been found that acidic residues in the region upstream of the cleavage site are required for efficient cleavage. See, e.g., Komoda et al. (1994) J. Virol. 68:7351-7357.

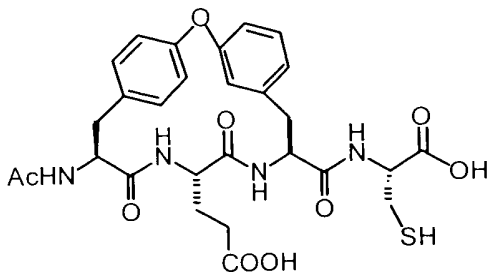
Inhibitors of HCV protease that have been reported include antioxidants (see, International Patent Application Publication No. WO 98/14181), certain peptides and peptide analogs (see, International Patent Application Publication No. WO 98/17679, Landro et al. (1997) Biochem. 36:9340-9348, Ingallinella et al.

(1998) Biochem. 37:8906-8914, Llinàs-Brunet et al. (1998) Bioorg. Med. Chem. Lett. 8:1713-1718), inhibitors based on the 70-amino acid polypeptide eglin c (Martin et al. (1998) Biochem. 37:11459-11468, inhibitors affinity selected from human pancreatic secretory trypsin inhibitor (hPSTI-C3) and minibody repertoires (MBip) (Dimasi et al. (1997) J. Virol. 71:7461-7469), cV_HE2 (a "camelized" variable domain antibody fragment) (Martin et al.(1997) Protein Eng. 10:607-614), and α1-antichymotrypsin (ACT) (Elzouki et al.) (1997) J. Hepat. 27:42-28). A ribozyme designed to selectively destroy hepatitis C virus RNA has recently been disclosed (see, *BioWorld Today* 9(217): 4 (November 10, 1998)).

Reference is also made to the PCT Publications, No. WO 98/17679, published April 30, 1998 (Vertex Pharmaceuticals Incorporated); WO 98/22496, published May 28, 1998 (F. Hoffmann-La Roche AG); and WO 99/07734, published February 18, 1999 (Boehringer Ingelheim Canada Ltd.).

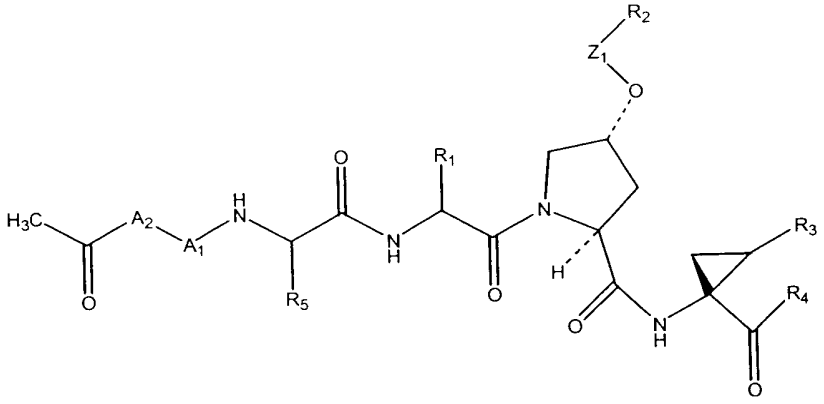
HCV has been implicated in cirrhosis of the liver and in induction of hepatocellular carcinoma. The prognosis for patients suffering from HCV infection is currently poor. HCV infection is more difficult to treat than other forms of hepatitis due to the lack of immunity or remission associated with HCV infection. Current data indicates a less than 50% survival rate at four years post cirrhosis diagnosis. Patients diagnosed with localized resectable hepatocellular carcinoma have a five-year survival rate of 10-30%, whereas those with localized unresectable hepatocellular carcinoma have a five-year survival rate of less than 1%.

Reference is made to A. Marchetti *et al*, *Synlett*, S1, 1000-1002 (1999) describing the synthesis of bicylic analogs of an inhibitor of HCV NS3 protease. A compound disclosed therein has the formula:

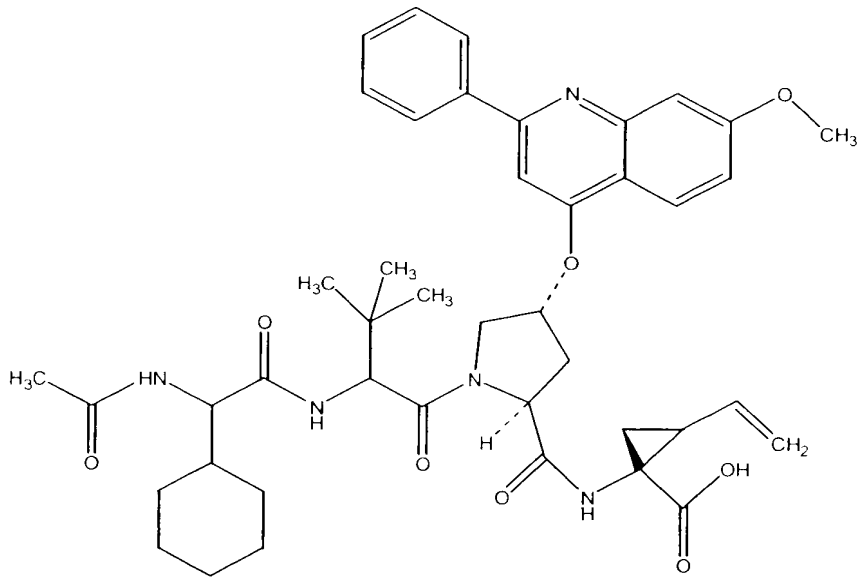


Reference is also made to W. Han *et al*, *Bioorganic & Medicinal Chem. Lett,* (2000) 10, 711-713, which describes the preparation of certain α-ketoamides, α-ketoesters and α-diketones containing allyl and ethyl functionalities.

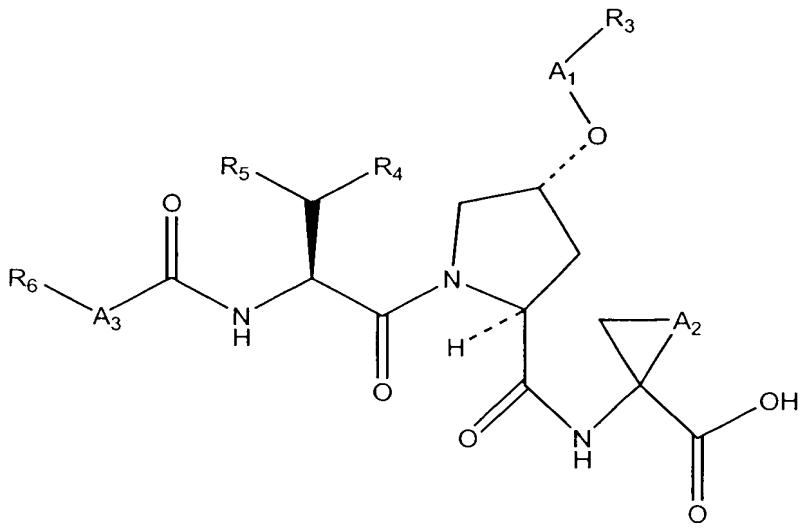
Reference is also made to WO 00/09558 (Assignee: Boehringer Ingelheim Limited; Published February 24, 2000) which discloses peptide derivatives of the formula:



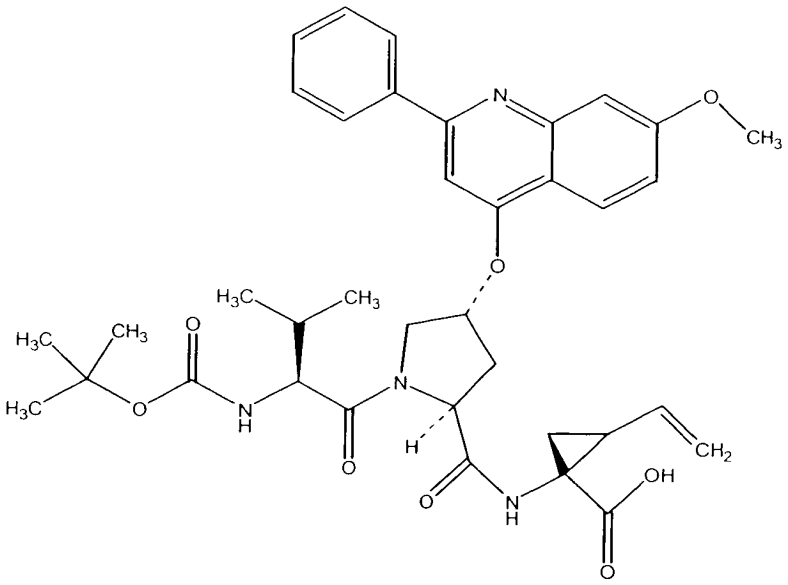
where the various elements are defined therein. An illustrative compound of that series is:



Reference is also made to WO 00/09543 (Assignee: Boehringer Ingelheim Limited; Published February 24, 2000) which discloses peptide derivatives of the formula:



where the various elements are defined therein. An illustrative compound of that series is:



Current therapies for hepatitis C include interferon-α (INF_{α}) and combination therapy with ribavirin and interferon. See, e.g., Beremguer et al. (1998) Proc. Assoc. Am. Physicians 110(2):98-112. These therapies suffer from a low sustained response rate and frequent side effects. See, e.g., Hoofnagle et al. (1997) N. Engl. J. Med. 336:347. Currently, no vaccine is available for HCV infection.

Pending and copending U. S. patent applications, Serial No. 60/194,607, filed April 5, 2000, and Serial No. 60/198,204, filed April 19, 2000, Serial No. 60/220,110, filed July 21, 2000, Serial No. 60/220,109, filed July 21, 2000, Serial No. 60/220,107, filed July 21, 2000, Serial No. 60/254,869, filed December 12, 2000, and Serial No. 60/220,101, filed July 21, 2000, disclose various types of peptides and/or other compounds as NS-3 serine protease inhibitors of hepatitis C virus.

There is a need for new treatments and therapies for HCV infection. It is, therefore, an object of this invention to provide compounds useful in the treatment or prevention or amelioration of one or more symptoms of hepatitis C.

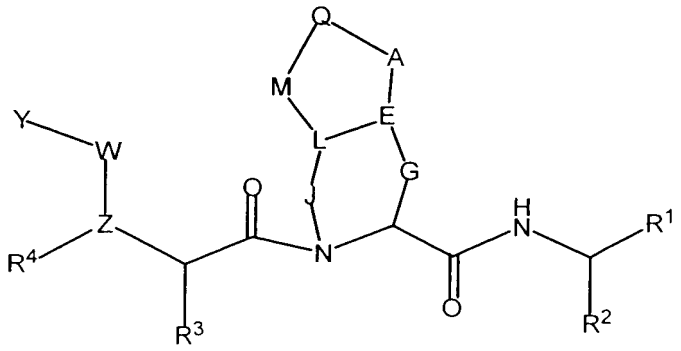
It is a further object herein to provide methods of treatment or prevention or amelioration of one or more symptoms of hepatitis C.

A still further object of the present invention is to provide methods for modulating the activity of serine proteases, particularly the HCV NS3/NS4a serine protease, using the compounds provided herein.

Another object herein is to provide methods of modulating the processing of the HCV polypeptide using the compounds provided herein.

Summary of the invention

In its many embodiments, the present invention provides a novel class of inhibitors of the HCV protease, pharmaceutical compositions containing one or more of the compounds, methods of preparing pharmaceutical formulations comprising one or more such compounds, and methods of treatment, prevention or amelioration or one or more of the symptoms of hepatitis C. Also provided are methods of modulating the interaction of an HCV polypeptide with HCV protease. Among the compounds provided herein, compounds that inhibit HCV NS3/NS4a serine protease activity are preferred. The present application discloses a compound, including enantiomers, stereoisomers, rotamers, tautomers, racemates and prodrug of said compound, and pharmaceutically acceptable salts or solvates of said compound, or of said prodrug, said compound having the general structure shown in Formula I:



Formula I

wherein:

Y is selected from the group consisting of the following moieties: alkyl, alkyl-aryl, heteroalkyl, heteroaryl, aryl-heteroaryl, alkyl-heteroaryl, cycloalkyl, alkyloxy, alkyl-aryloxy, aryloxy, heteroaryloxy, heterocycloalkyloxy, cycloalkyloxy, , alkylamino, arylamino, alkyl-arylamino, arylamino, heteroarylamino, cycloalkylamino and heterocycloalkylamino, with the proviso that Y maybe optionally substituted with X^{11} or X^{12};

X^{11} is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, arylalkyl, heteroaryl, alkylheteroaryl, or heteroarylalkyl, with the proviso that X^{11} may be additionally optionally substituted with X^{12};

X^{12} is hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, alkylsulfonamido, arylsulfonamido, carboxy, carbalkoxy, carboxamido, alkoxycarbonylamino, alkoxycarbonyloxy, alkylureido, arylureido, halogen, cyano, or nitro, with the proviso that said alkyl, alkoxy, and aryl may be additionally optionally substituted with moieties independently selected from X^{12};

R^1 is COR^5 or $B(OR)_2$, wherein R^5 is H, OH, OR^8, NR^9R^{10}, CF_3, C_2F_5, C_3F_7, CF_2R^6, R^6, or COR^7 wherein R^7 is H, OH, OR^8, CHR^9R^{10}, or NR^9R^{10}, wherein R^6, R^8, R^9 and R^{10} are independently selected from the group consisting of H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, cycloalkyl, arylalkyl, heteroarylalkyl, $[CH(R^{1'})]_pCOOR^{11}$, $[CH(R^{1'})]_pCONR^{12}R^{13}$, $[CH(R^{1'})]_pSO_2R^{11}$, $[CH(R^{1'})]_pCOR^{11}$, $[CH(R^{1'})]_pCH(OH)R^{11}$, $CH(R^{1'})CONHCH(R^{2'})COO\ R^{11}$, $CH(R^{1'})CONHCH(R^{2'})CONR^{12}R^{13}$, $CH(R^{1'})CONHCH(R^{2'})R'$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})COO\ R^{11}$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONR^{12}R^{13}$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONHCH(R^{4'})COO\ R^{11}$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONHCH(R^{4'})CONR^{12}R^{13}$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONHCH(R^{4'})CONHCH(R^{5'})COO\ R^{11}$

and $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONHCH(R^{4'})CONHCH(R^{5'})CONR^{12}R^{13}$, wherein $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$, $R^{5'}$, R^{11}, R^{12}, R^{13}, and R' are independently selected from the group consisting of H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, alkyl-aryl, alkyl-heteroaryl, aryl-alkyl and heteroaralkyl;

Z is selected from O, N, CH or CR;

W may be present or absent, and if W is present, W is selected from C=O, C=S, C(=N-CN), or SO_2;

Q may be present or absent, and when Q is present, Q is CH, N, P, $(CH_2)_p$, $(CHR)_p$, $(CRR')_p$, O, NR, S, or SO_2; and when Q is absent, M may be present or absent; when Q and M are absent, A is directly linked to L;

A is O, CH_2, $(CHR)_p$, $(CHR\text{-}CHR')_p$, $(CRR')_p$, NR, S, SO_2 or a bond;

E is CH, N, CR, or a double bond towards A, L or G;

G may be present or absent, and when G is present, G is $(CH_2)_p$, $(CHR)_p$, or $(CRR')_p$; and when G is absent, J is present and E is directly connected to the carbon atom in Formula I as G is linked to;

J maybe present or absent, and when J is present, J is $(CH_2)_p$, $(CHR)_p$, or $(CRR')_p$, SO_2, NH, NR or O; and when J is absent, G is present and E is directly linked to N shown in Formula I as linked to J;

L may be present or absent, and when L is present, L is CH, CR, O, S or NR; and when L is absent, then M may be present or absent; and if M is present with L being absent, then M is directly and independently linked to E, and J is directly and independently linked to E;

M may be present or absent, and when M is present, M is O, NR, S, SO_2, $(CH_2)_p$, $(CHR)_p$ $(CHR\text{-}CHR')_p$, or $(CRR')_p$;

p is a number from 0 to 6; and

R, R', R^2, R^3 and R^4 are independently selected from the group consisting of H; C_1-C_{10} alkyl; C_2-C_{10} alkenyl; C_3-C_8 cycloalkyl; C_3-C_8 heterocycloalkyl, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, nitro, halogen;

(cycloalkyl)alkyl and (heterocycloalkyl)alkyl, wherein said cycloalkyl is made of three to eight carbon atoms, and zero to six oxygen, nitrogen, sulfur, or phosphorus atoms, and said alkyl is of one to six carbon atoms; aryl; heteroaryl; alkyl-aryl; and alkyl-heteroaryl;

wherein said alkyl, heteroalkyl, alkenyl, heteroalkenyl, aryl, heteroaryl, cycloalkyl and heterocycloalkyl moieties may be optionally and chemically-suitably substituted, with said term "substituted" referring to optional and chemically-suitable substitution with one or more moieties selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, aralkyl, cycloalkyl, heterocyclic, halogen, hydroxy, thio, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, nitro, sulfonamido, sulfoxide, sulfone, sulfonyl urea, hydrazide, and hydroxamate;

further wherein said unit N-C-G-E-L-J-N represents a five-membered or six-membered cyclic ring structure with the proviso that when said unit N-C-G-E-L-J-N represents a five-membered cyclic ring structure, or when the bicyclic ring structure in Formula I comprising N, C, G, E, L, J, N, A, Q, and M represents a five-membered cyclic ring structure, then said five-membered cyclic ring structure lacks a carbonyl group as part of the cyclic ring.

Among the above-stated definitions for the various moieties of Formula I, the preferred groups for the various moieties are as follows:

Preferred definition for R^1 is COR^5 with R^5 being H, OH, $COOR^8$ or $CONR^9R^{10}$, where R^8, R^9 and R^{10} are defined above. Still preferred moiety for R^1 is $COCONR^9R^{10}$, where R^9 is H; and R^{10} is H, R^{14}, $[CH(R^{1'})]_pCOOR^{11}$, $[CH(R^{1'})]_pCONR^{12}R^{13}$, $[CH(R^{1'})]_pSO_2R^{11}$, $[CH(R^{1'})]_pSO_2N\ R^{12}R^{13}$, $[CH(R^{1'})]_pCOR^{11}$, $CH(R^{1'})CONHCH(R^{2'})COOR^{11}$, $CH(R^{1'})CONHCH(R^{2'})\ CONR^{12}R^{13}$, or $CH(R^{1'})CONHCH(R^{2'})(R')$, wherein R^{14} is H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, alkyl-aryl, alkyl-heteroaryl, aryl-alkyl, alkenyl, alkynyl or heteroaralkyl.

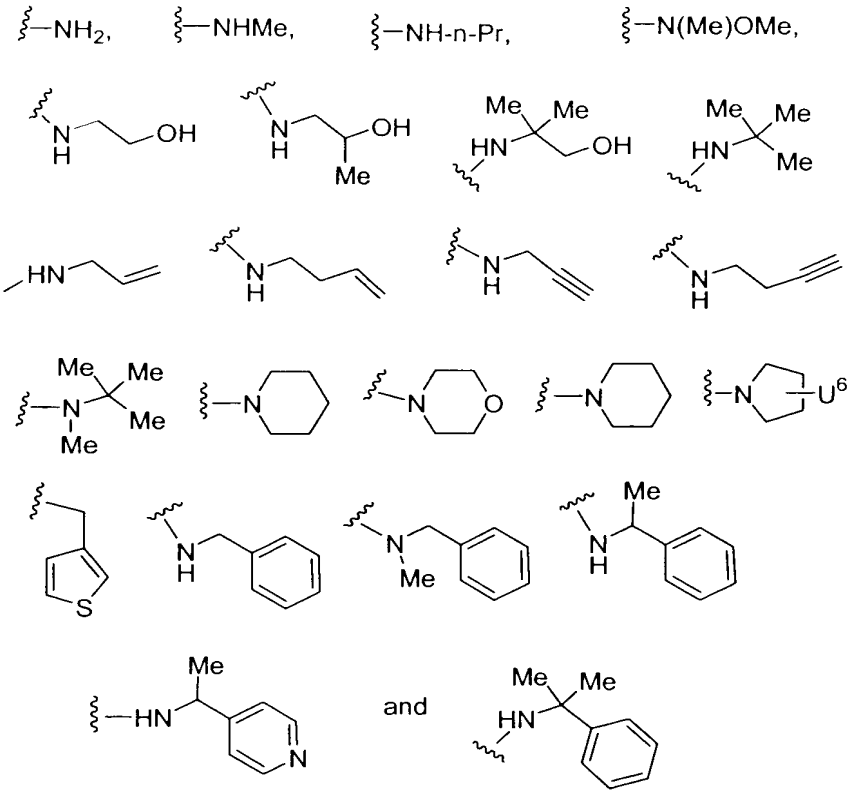
Among the above for R^{10}, preferred moieties for R^{10} are: H, R^{14}, $CH(R^{1'})COOR^{11}$, $CH(R^{1'})CH(R^{1'})COOR^{11}$, $CH(R^{1'})CONR^{12}R^{13}$, $CH(R^{1'})CH(R^{1'})CONR^{12}R^{13}$, $CH(R^{1'})CH(R^{1'})SO_2R^{11}$, $CH(R^{1'})CH(R^{1'})SO_2N\ R^{12}R^{13}$,

$CH(R^{1'})CH(R^{1'})COR^{11}$, $CH(R^{1'})CONHCH(R^{2'})COOR^{11}$, $CH(R^{1'})CONHCH(R^{2'})CONR^{12}R^{13}$, or $CH(R^{1'})CONHCH(R^{2'})(R')$, wherein $R^{1'}$ is H or alkyl, and $R^{2'}$ is phenyl, substituted phenyl, hetero atom-substituted phenyl, thiophenyl, cycloalkyl, piperidyl or pyridyl.

More preferred moieties are: for $R^{1'}$ is H, for R^{11} is H, methyl, ethyl, allyl, *tert*-butyl, benzyl, α-methylbenzyl, α,α-dimethylbenzyl, 1-methylcyclopropyl or 1-methylcyclopentyl; for

R' is hydroxymethyl or $CH_2CONR^{12}R^{13}$ where

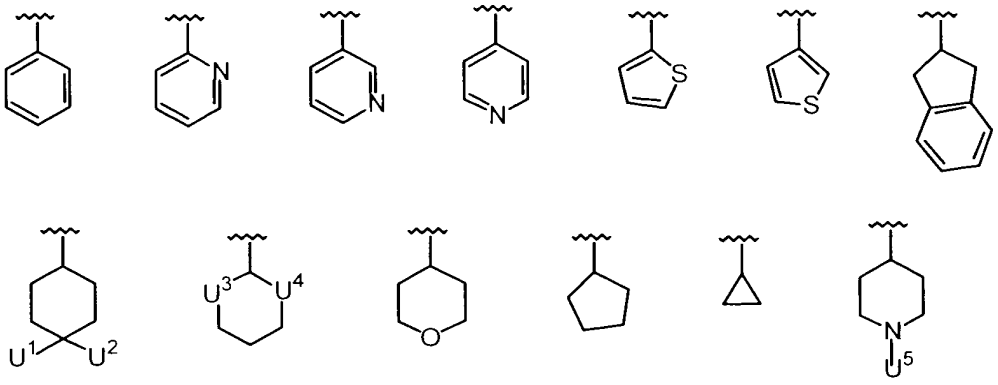
$NR^{12}R^{13}$ is selected from the group consisting of:



wherein U^6 is H, OH, or CH_2OH;

R^{14} is preferably selected from the group consisting of: H, Me, Et, *n*-propyl, methoxy, cyclopropyl, *n*-butyl, 1-but-3-ynyl, benzyl, α-methylbenzyl, phenethyl, allyl, 1-but-3-enyl, OMe, cyclopropylmethyl;

and $R^{2'}$ is preferably independently selected from the group consisting of:



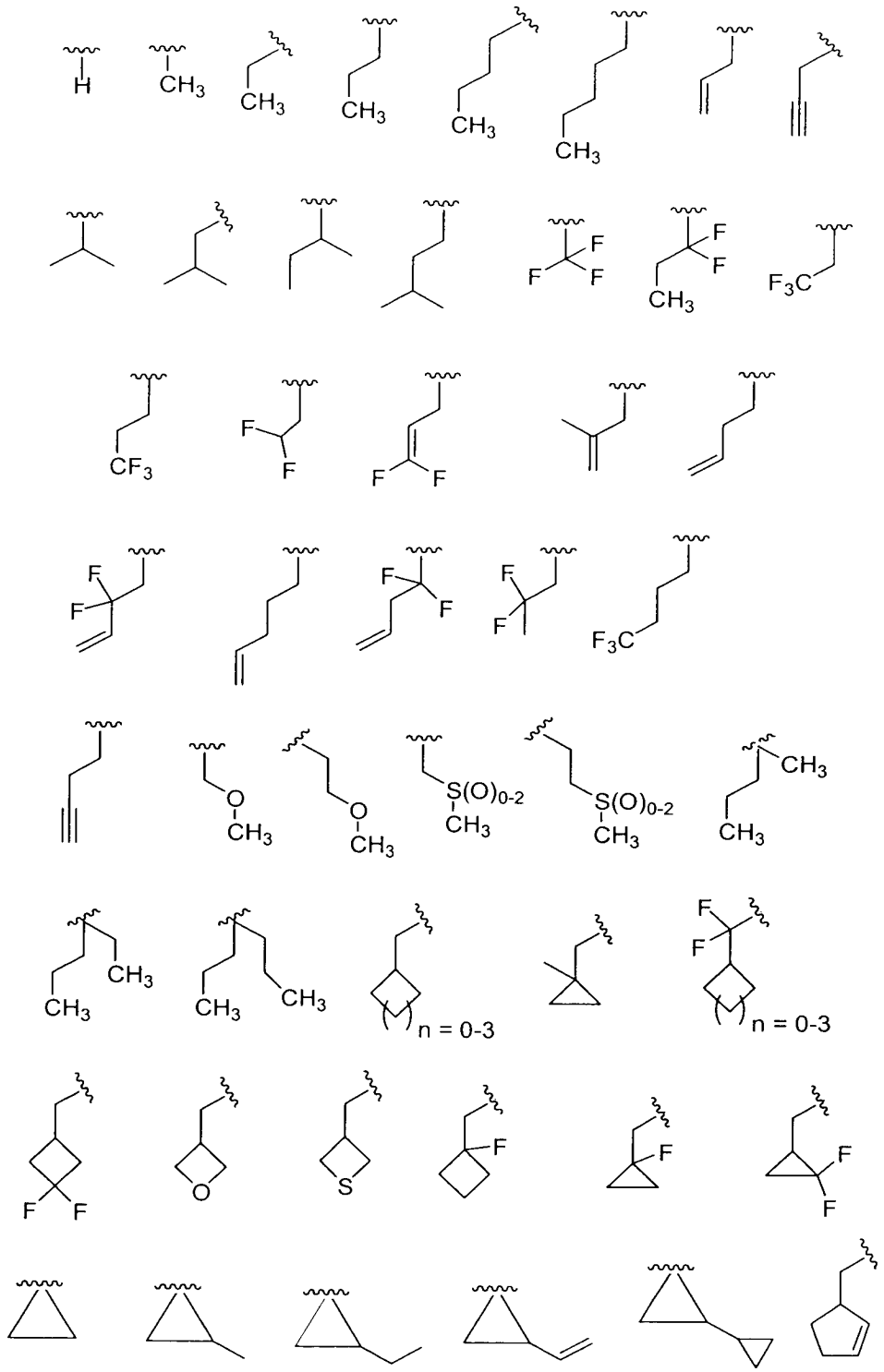
wherein:

U^1 and U^2 maybe same or different and are selected from H, F, CH_2COOH, CH_2COOMe, CH_2CONH_2, $CH_2CONHMe$, CH_2CONMe_2, azido, amino, hydroxyl, substituted amino, substituted hydroxyl;

U^3 and U^4 maybe same or different and are selected from O and S;

U^5 is selected from the moieties consisting of alkyl sulfonyl, aryl sulfonyl, heteroalkyl sulfonyl, heteroaryl sulfonyl, alkyl carbonyl, aryl carbonyl, heteroalkyl carbonyl, heteroaryl carbonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl or a combination thereof.

Preferred moieties for R^2 are:


H
CH3
CH3
CH3
CH3
CH3
F
F
F
F
CH3
F3C
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F
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F3C
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CH3
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S(O)0-2
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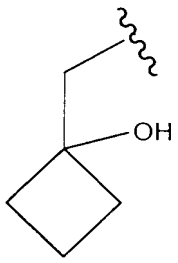
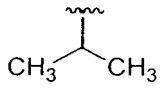
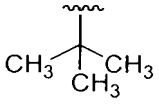
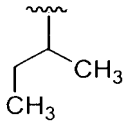
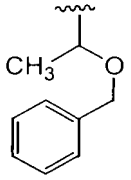


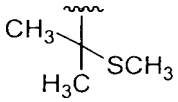
Preferred moieties for R^3 are:

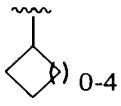


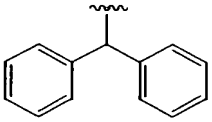


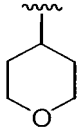


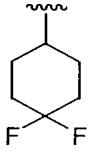


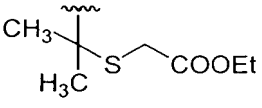


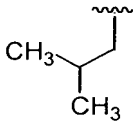


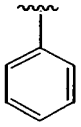


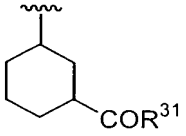


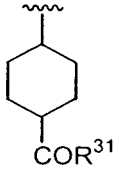


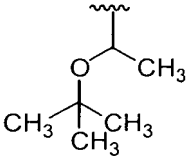


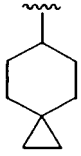


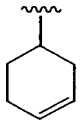




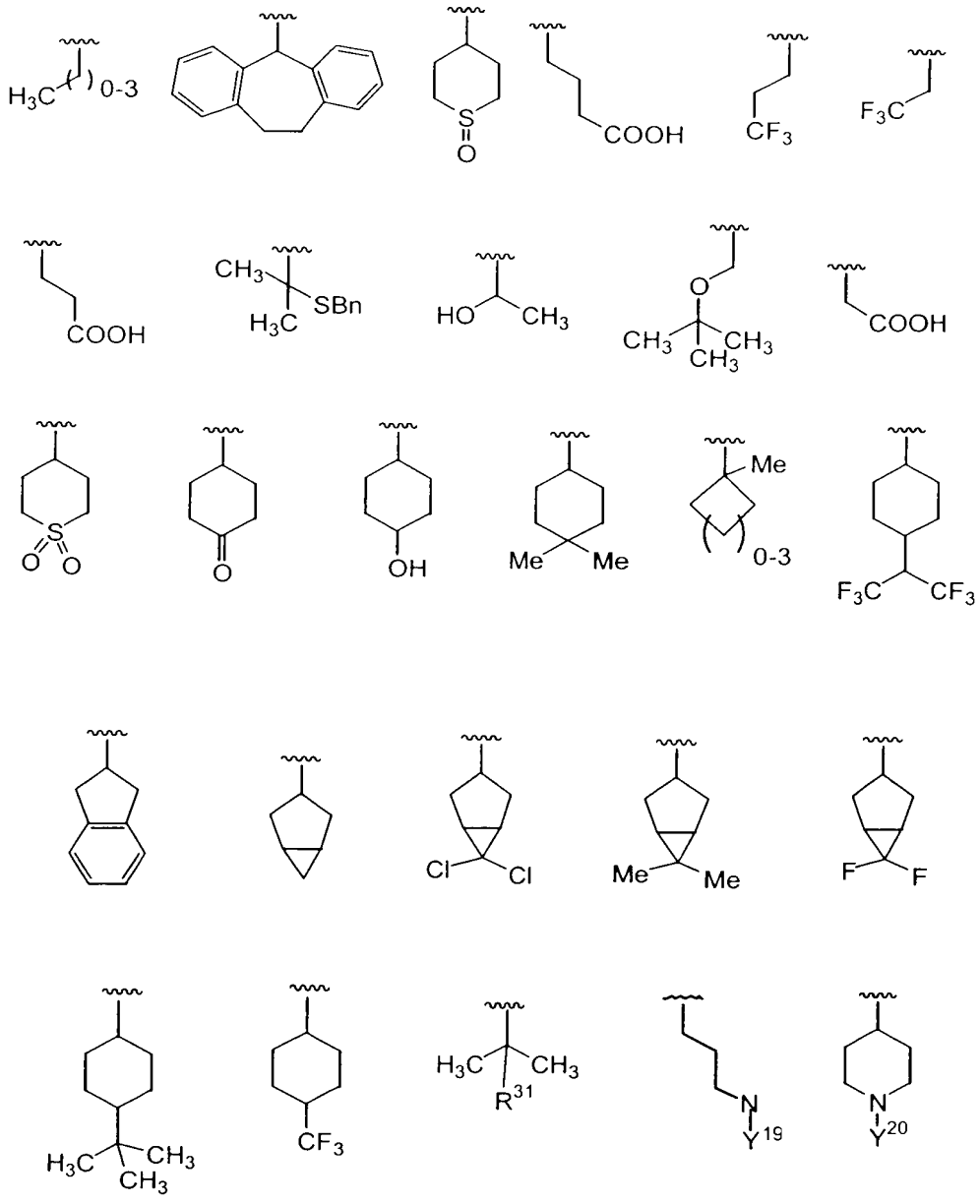






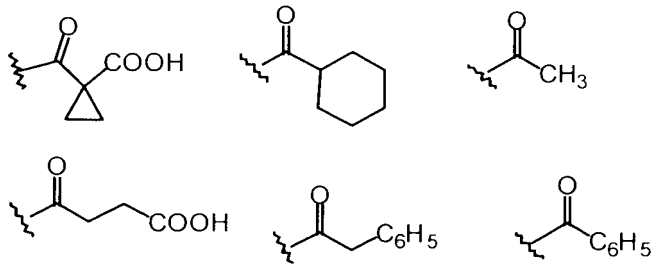


5

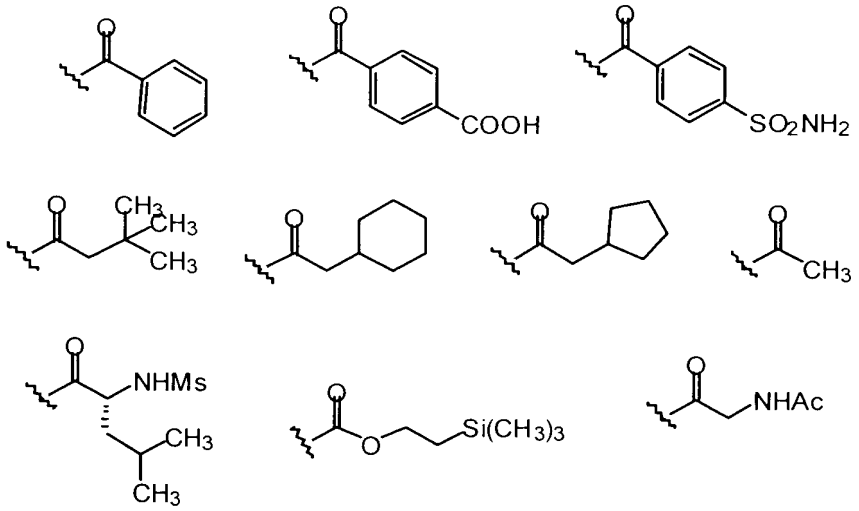


wherein R^{31} = OH or O-alkyl;

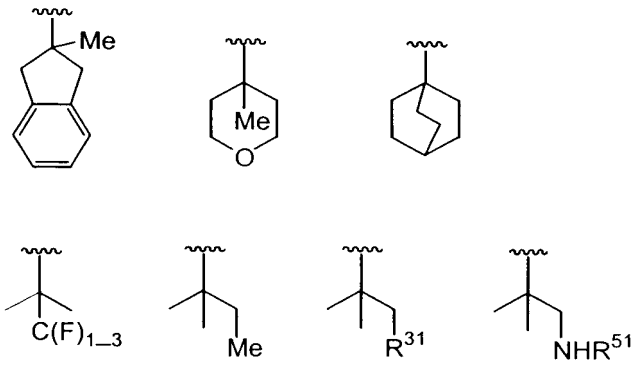
Y^{19} is selected from the following moieties:



and Y^{20} is selected from the following moieties:

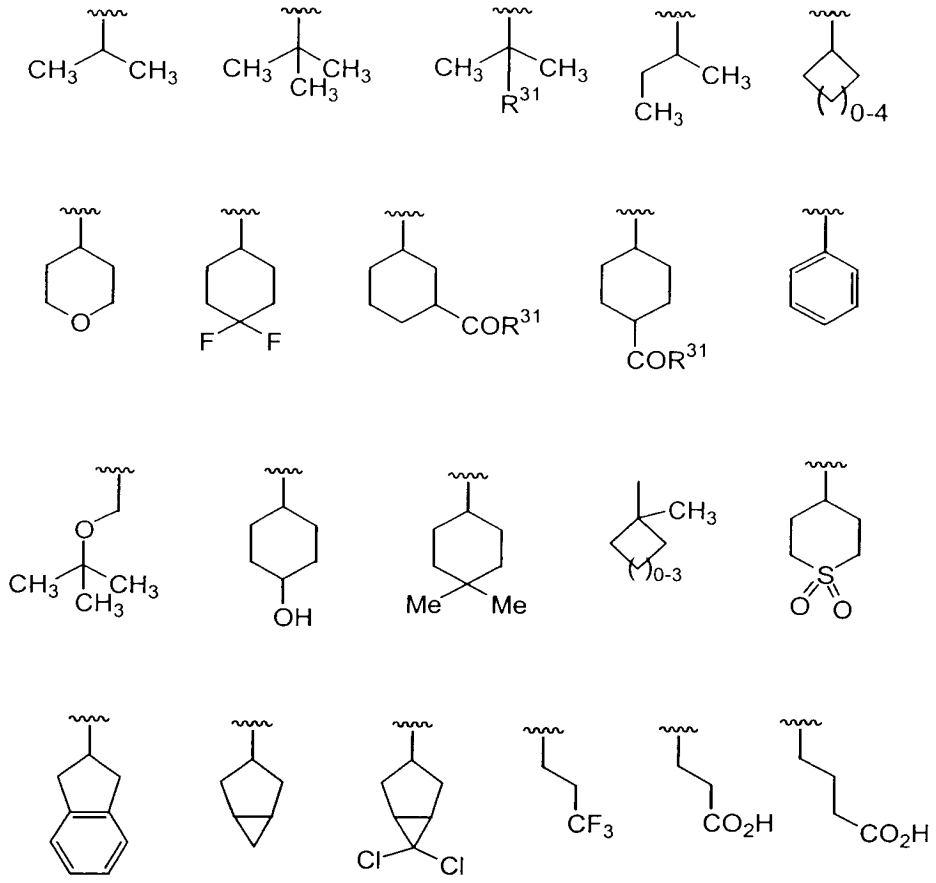


Additional R^3 moieties include the following:

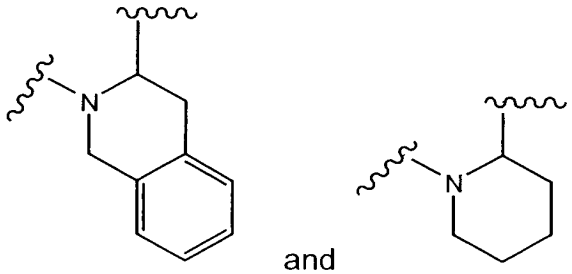


where R^{51}= H, -$COCH_3$, -COOtBu or -CONHtBu.

Most preferred moieties for R^3 are:

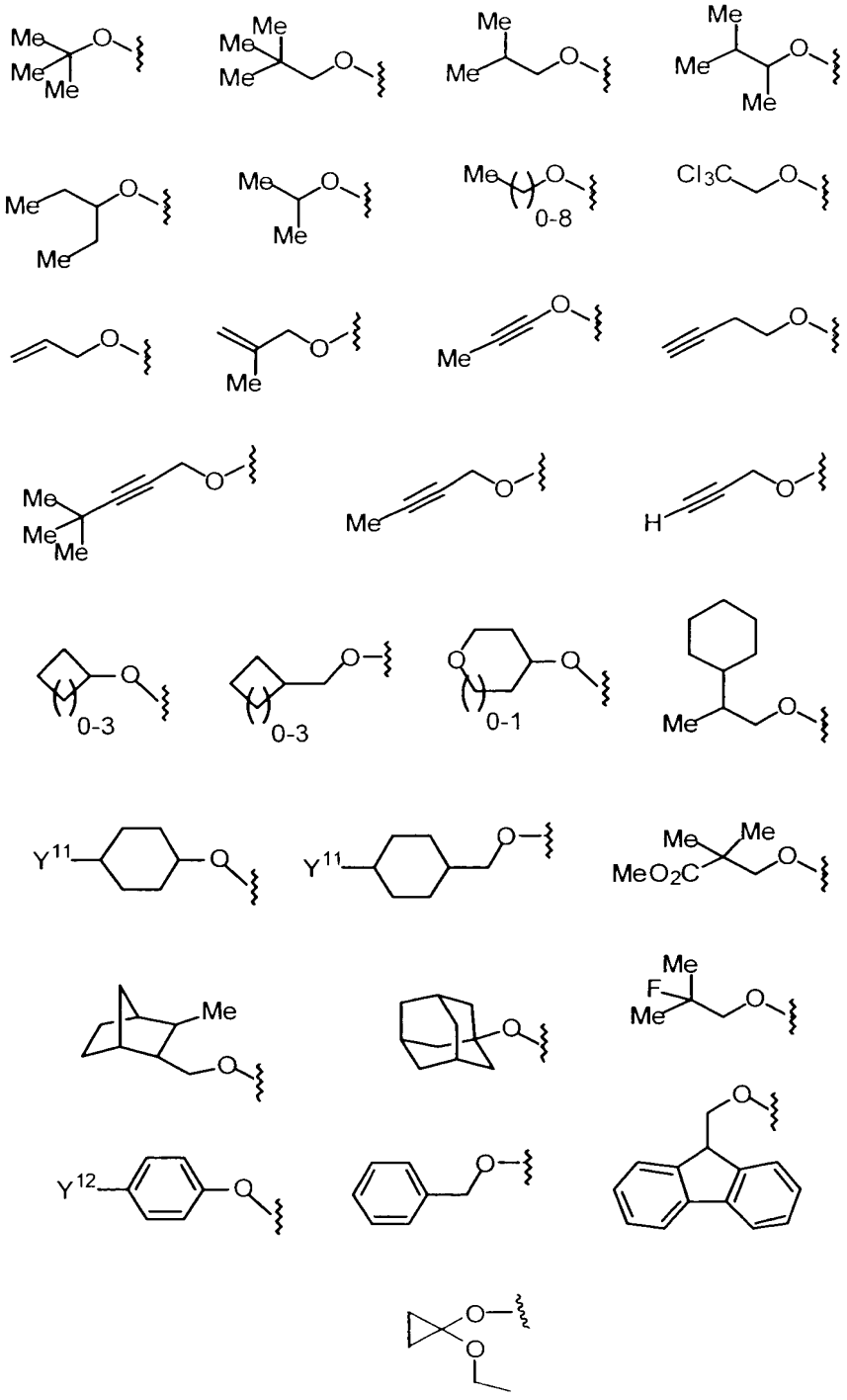


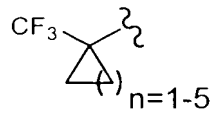
Some other preferred moieties are: for Z it is N, for R^4 it is H, and for W it is C=O. Additionally, the moiety Z-C-R^3 in Formula I, with R^4 being absent, may be represented by the following structures:

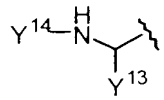


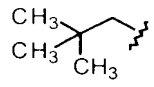
and

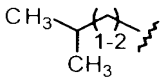
Preferred moieties for Y are:

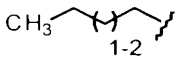


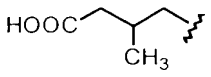

CF3
n=1-5

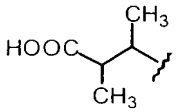

Y14
H
N
Y13

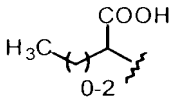

CH3
CH3
CH3

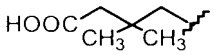

CH3
1-2
CH3

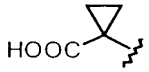

CH3
1-2

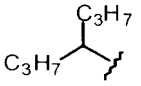

HOOC
CH3

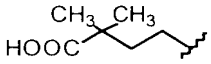

HOOC
CH3
CH3

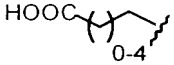

COOH
H3C
0-2

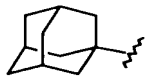

HOOC
CH3
CH3

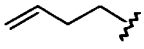

HOOC

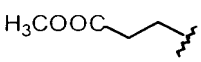

C3H7
C3H7

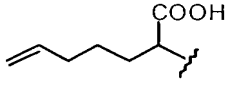

CH3
CH3
HOOC

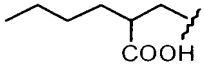

HOOC
0-4

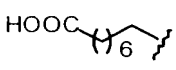


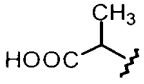


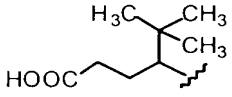

H3COOC

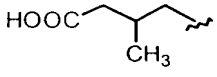

COOH

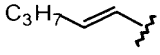

COOH

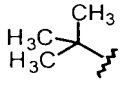

HOOC
6

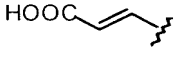

CH3
HOOC

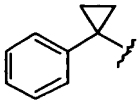

H3C
CH3
CH3
HOOC

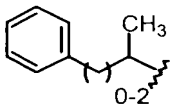

HOOC
CH3

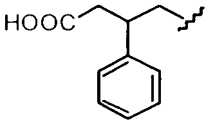

C3H7

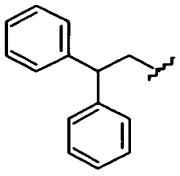

CH3
H3C
H3C

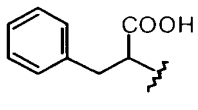

HOOC

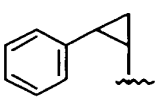


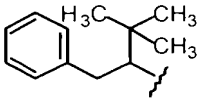

CH3
0-2

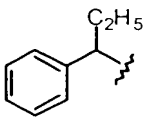

HOOC

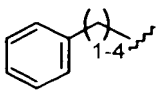


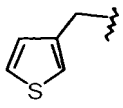

COOH

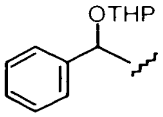


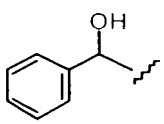

H3C
CH3
CH3

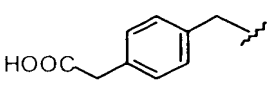

C2H5

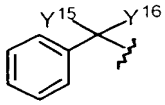

1-4

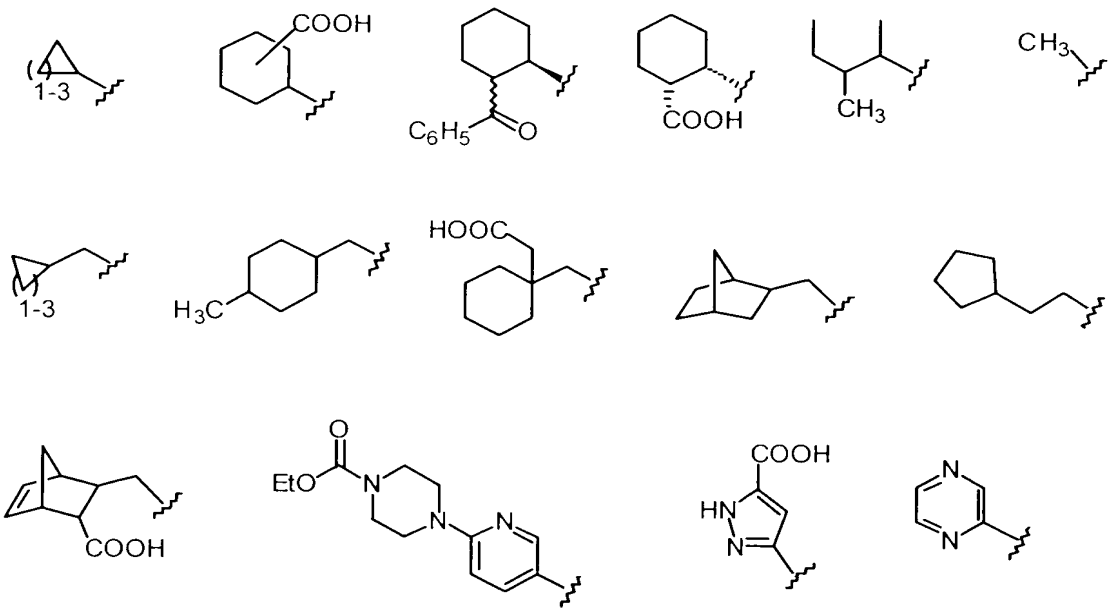

S

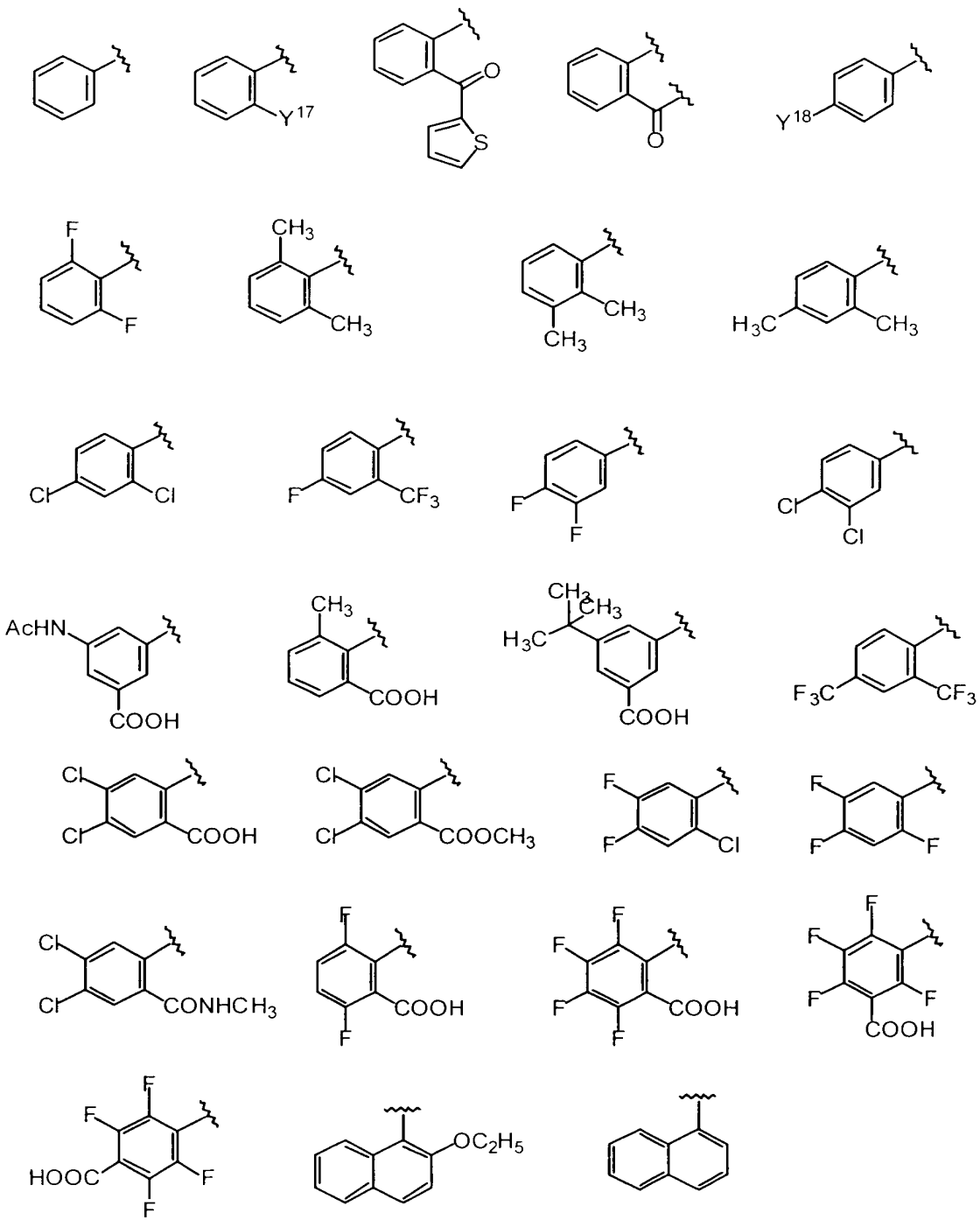

OTHP

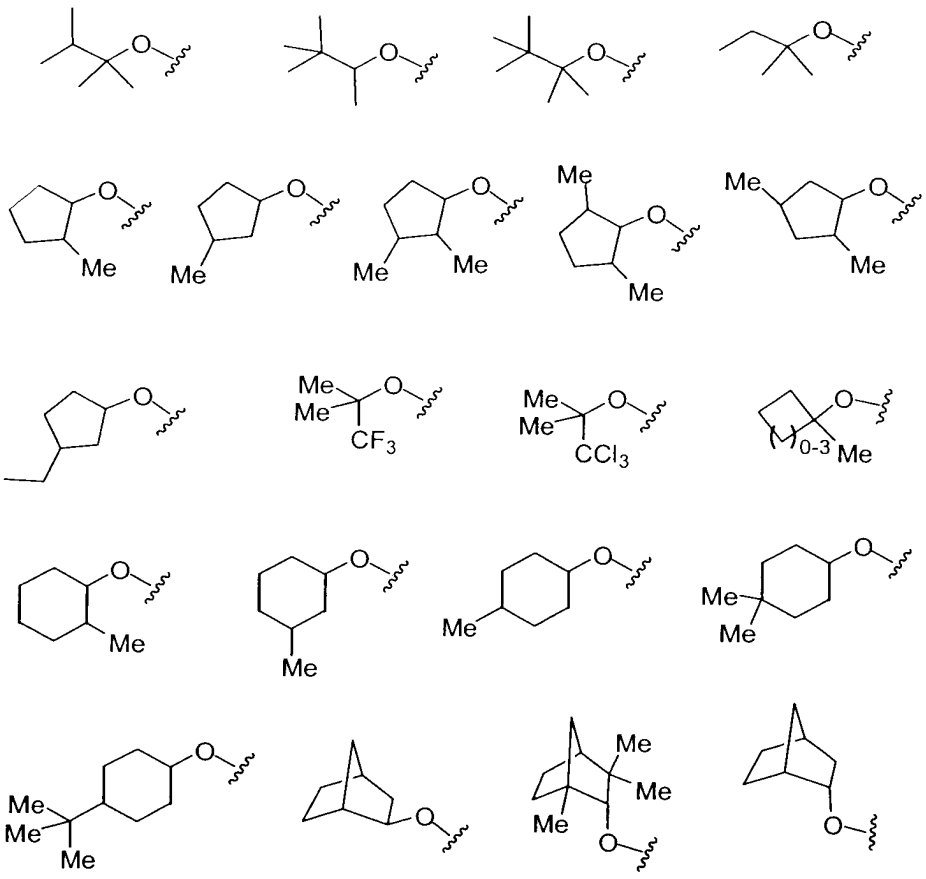

OH

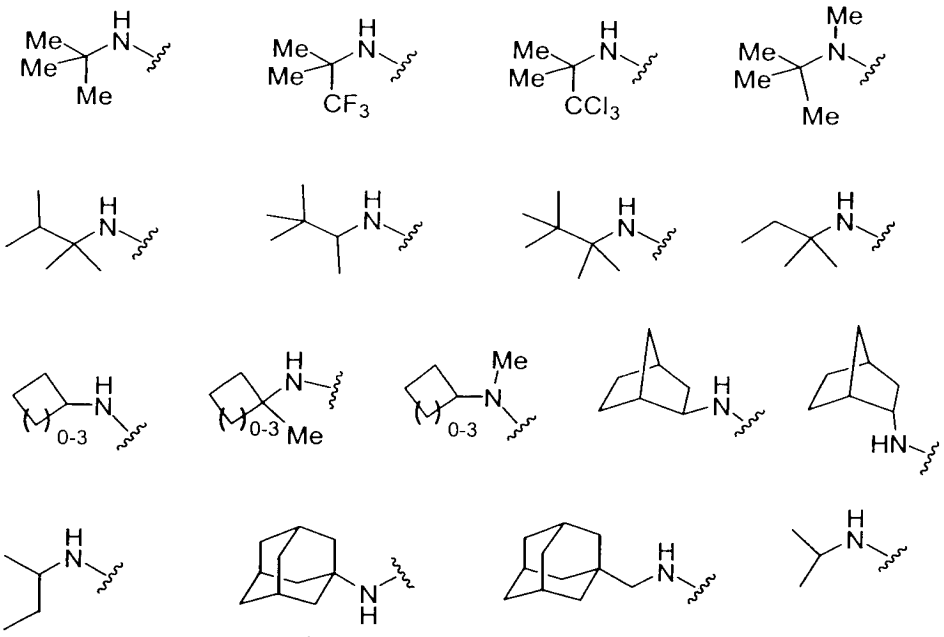

HOOC


Y15
Y16


1-3
COOH
C_6H_5
O
COOH
CH_3
CH_3
1-3
H_3C
HOOC
COOH
EtO
O
N
N
N
COOH
HN
N
N
N


Y17
O
S
O
Y18
F
F
CH3
CH3
CH3
CH3
CH3
H3C
CH3
Cl
Cl
F
CF3
F
F
Cl
Cl
AcHN
COOH
CH3
COOH
CH3
CH3
H3C
COOH
F3C
CF3
Cl
Cl
COOH
Cl
Cl
COOCH3
F
F
Cl
F
F
F
Cl
Cl
CONHCH3
F
COOH
F
F
F
F
COOH
F
F
F
F
F
COOH
F
F
HOOC
F
F
OC2H5


O
Me
CF3
CCl3
0-3

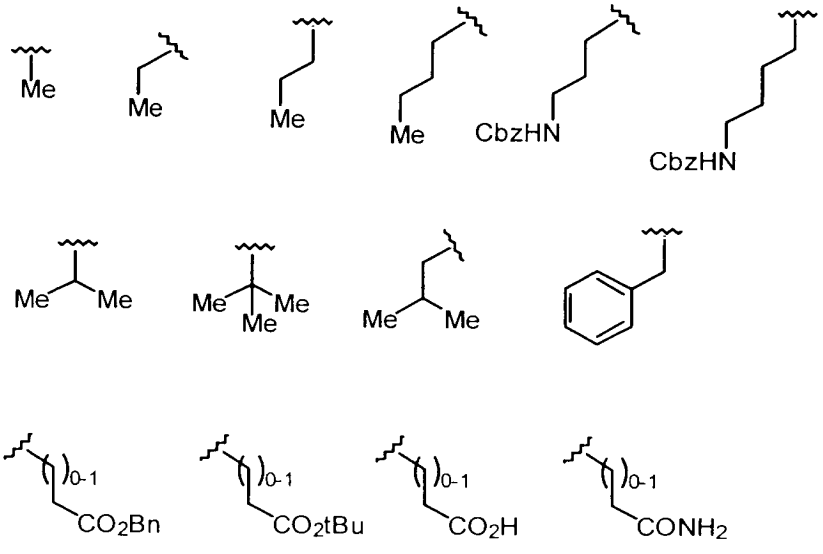


wherein:

Y^{11} is selected from H, COOH, COOEt, OMe, Ph, OPh, NHMe, NHAc, NHPh, $CH(Me)_2$, 1-triazolyl, 1-imidazolyl, and $NHCH_2COOH$;

Y^{12} is selected from H, COOH, COOMe, OMe, F, Cl, or Br;

Y^{13} is selected from the following moieties:



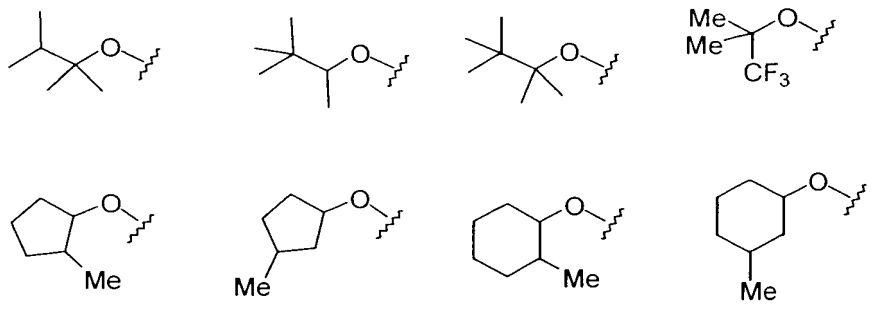
Y^{14} is selected from $MeSO_2$, Ac, Boc, iBoc, Cbz, or Alloc;

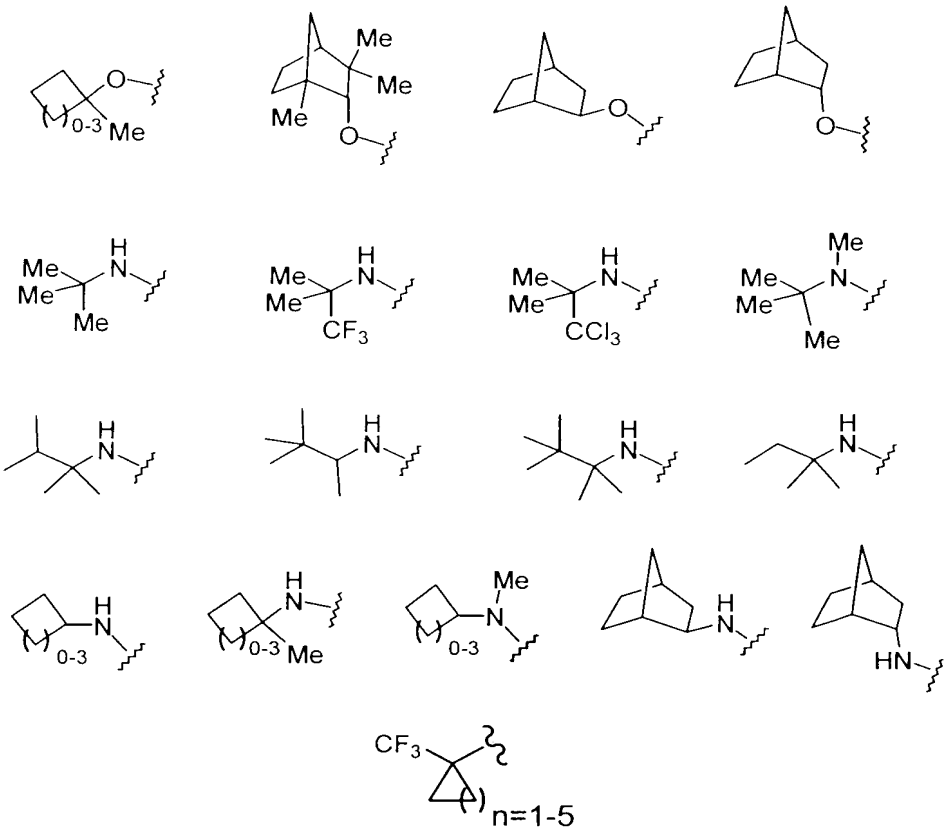
Y^{15} and Y^{16} are independently selected from alkyl, aryl, heteroalkyl, and heteroaryl;

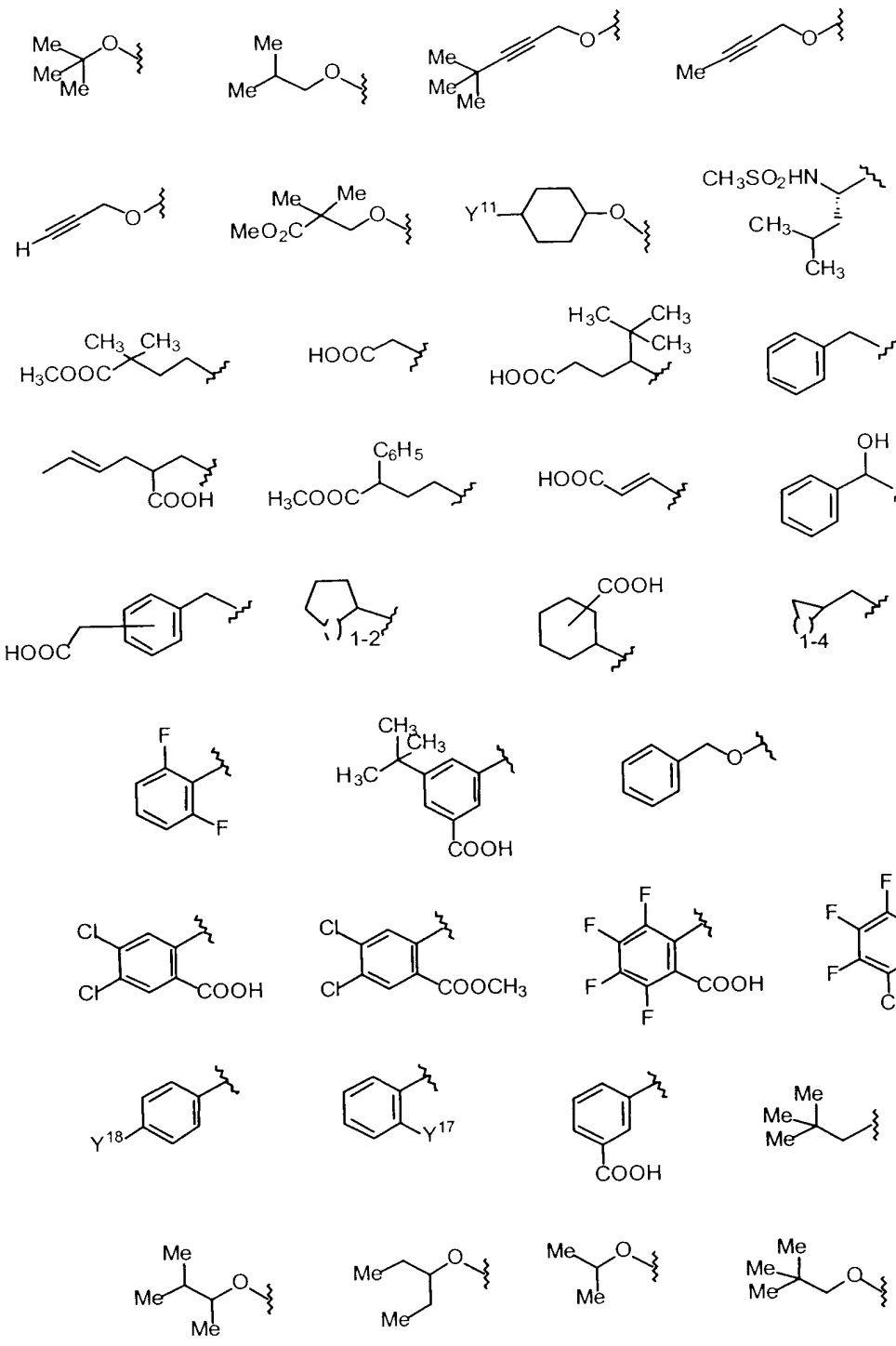
Y^{17} is CF_3, NO_2, $CONH_2$, OH, $COOCH_3$, OCH_3, OC_6H_5, C_6H_5, COC_6H_5, NH_2, or COOH; and

Y^{18} is $COOCH_3$, NO_2, $N(CH_3)_2$, F, OCH_3, CH_2COOH, COOH, SO_2NH_2, or $NHCOCH_3$.

Y may be more preferably represented by:

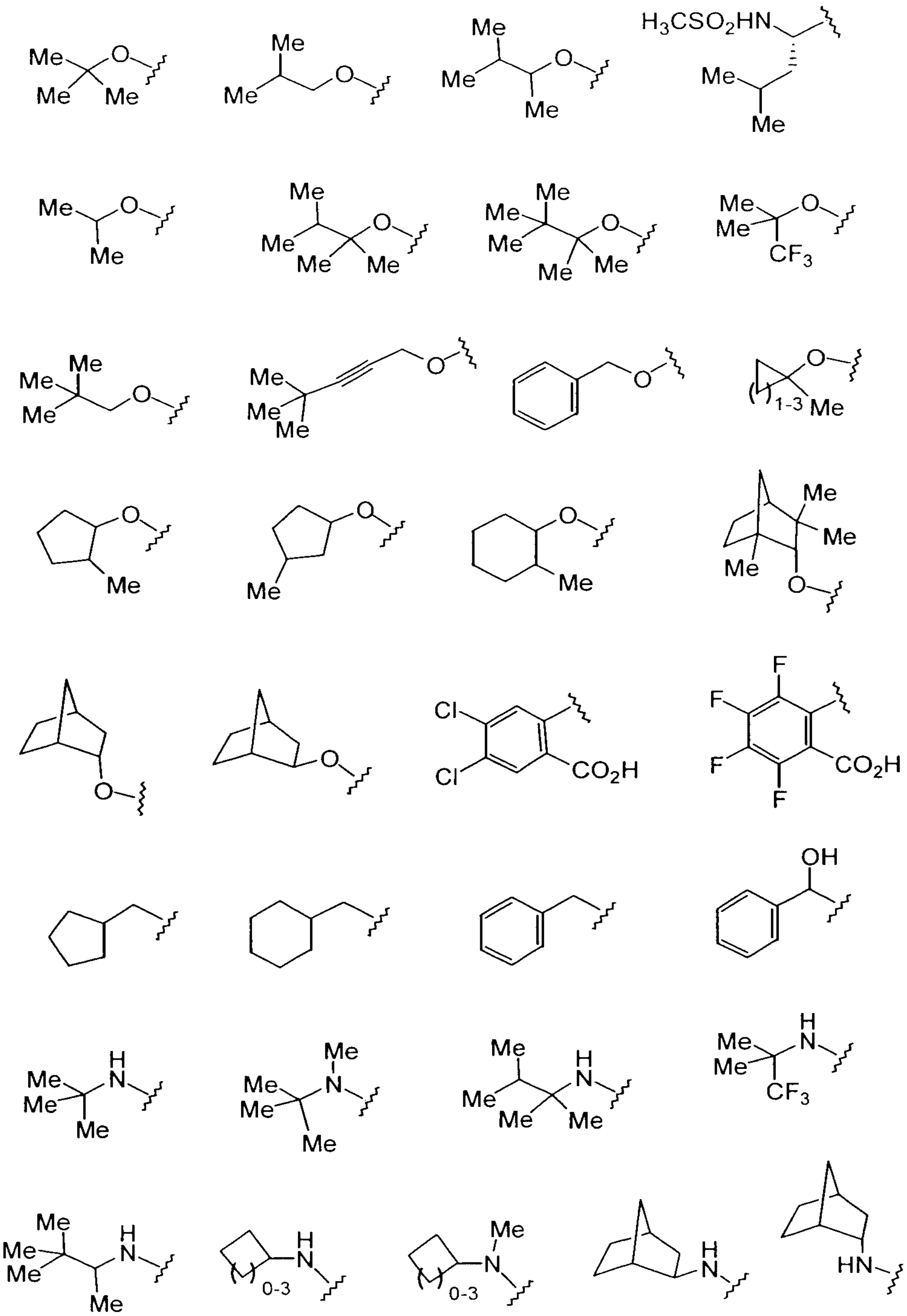



O
0-3
Me
Me
Me
Me
O
O
O
H
N
Me
Me
Me
Me
Me
CF3
Me
Me
CCl3
Me
Me
N
Me
H
N
H
N
H
N
H
N
H
N
0-3
H
N
0-3
Me
Me
N
0-3
H
N
H
N
HN
CF3
n=1-5

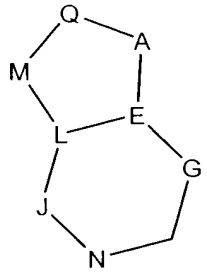


wherein:
Y^{17} = CF_3, NO_2, $CONH_2$, OH, NH_2, or COOH;
Y^{18}= F, COOH,

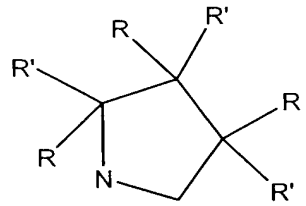
Still more preferred moieties for Y are:



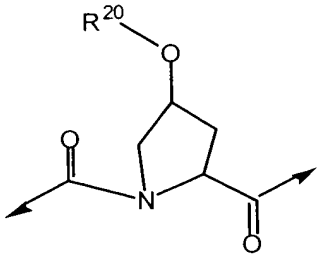
As shown in Formula I, the unit:



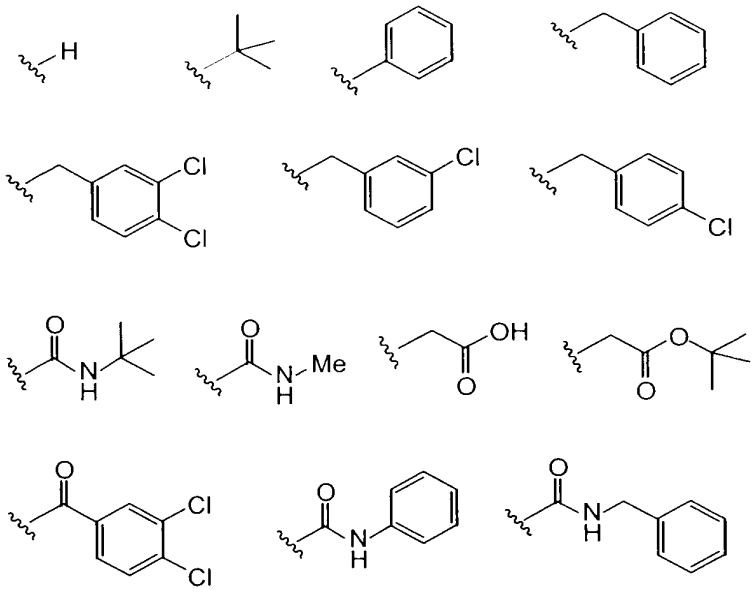
represents a cyclic ring structure, which may be a five-membered or six-membered ring structure. When that cyclic ring represents a five-membered ring, it is a requirement of this invention that that five-membered cyclic ring does not contain a carbonyl group as part of the cyclic ring structure. Preferably, that five-membered ring is of the structure:



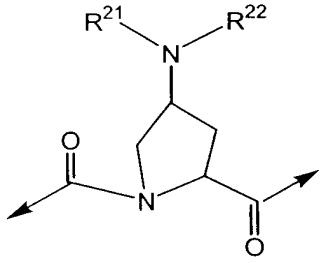
wherein R and R' are defined above. Preferred representations for that five-membered cyclic ring structure is:



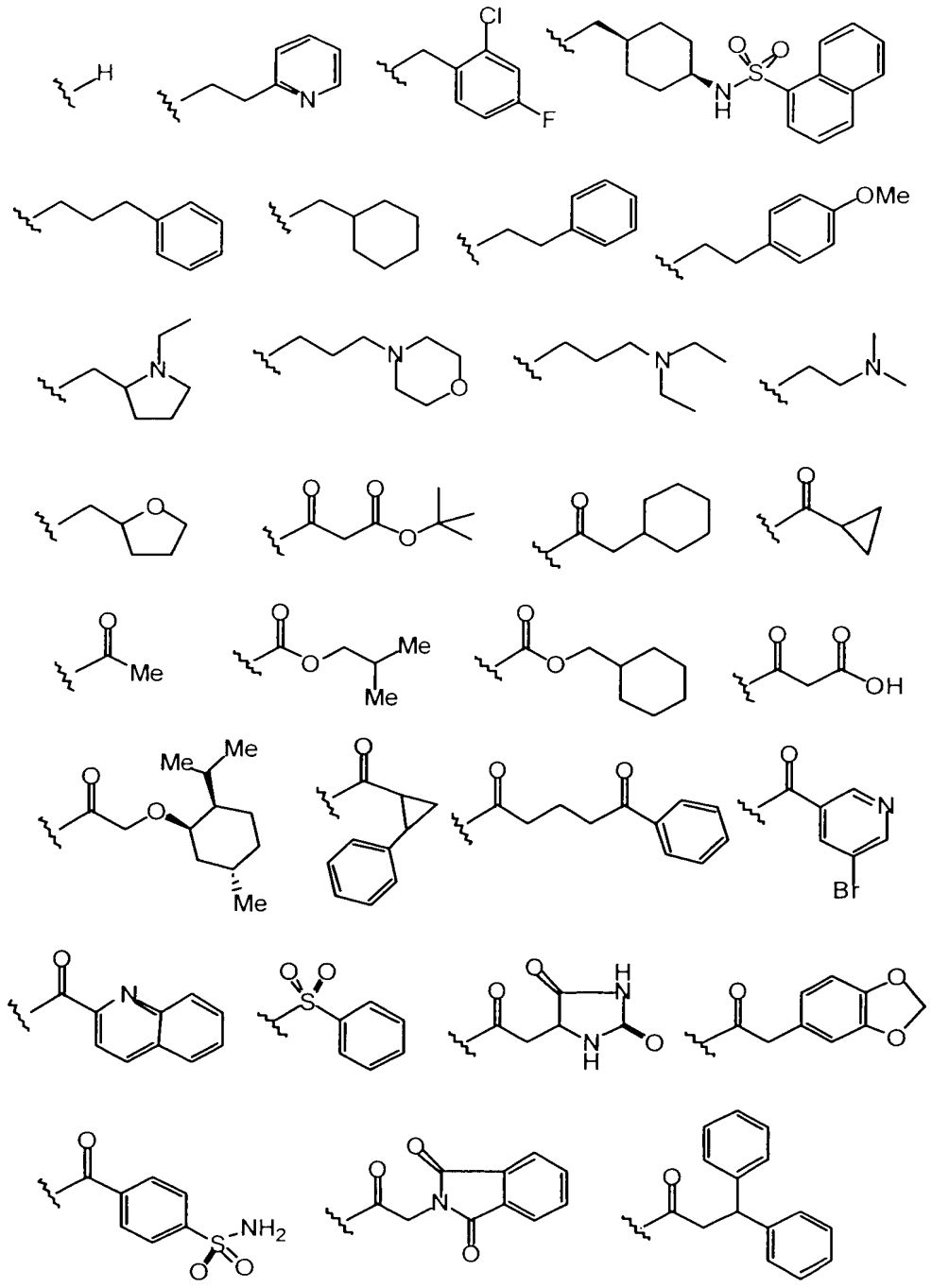
where R^{20} is selected from the following moieties:



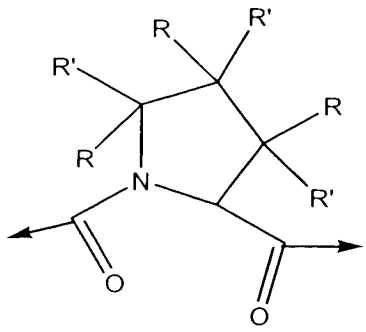
Furthermore, that five-membered ring, along with its adjacent two exocyclic carbonyls, may be represented as follows:



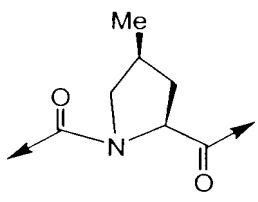
in which case, R^{21} and R^{22} may be the same or different and are independently selected from the following moieties:

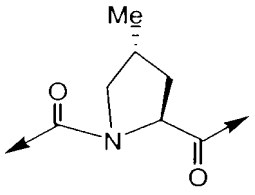


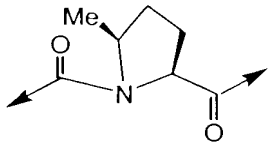
Some preferred illustrations for the five-membered ring structure:

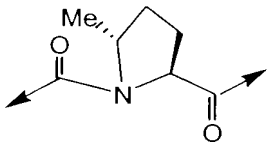


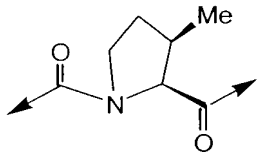
are as follows:

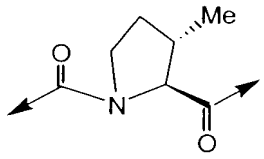

Me
O
N
O

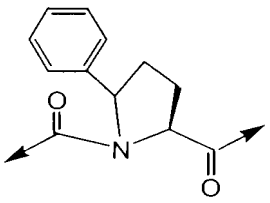

Me
O
N
O

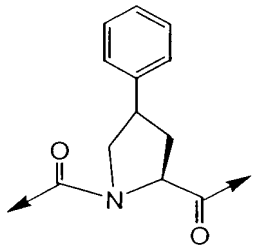

Me
O
N
O

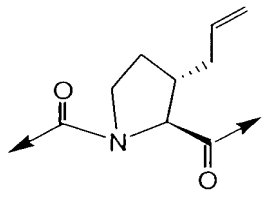

Me
O
N
O

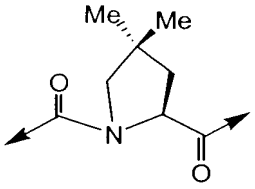

Me
O
N
O

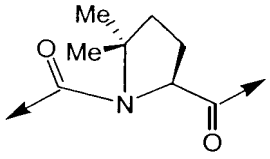

Me
O
N
O

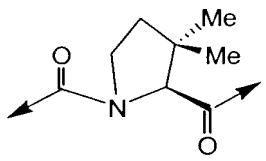

O
N
O

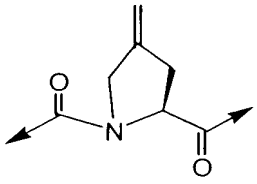

O
N
O

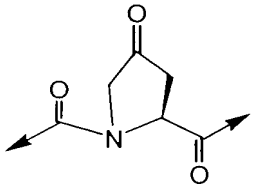

O
N
O

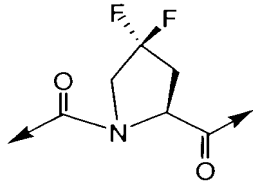

Me
Me
O
N
O

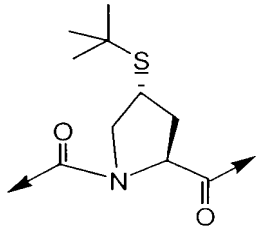

Me
Me
O
N
O

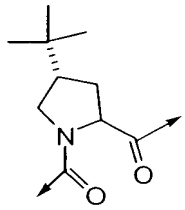

Me
Me
O
N
O

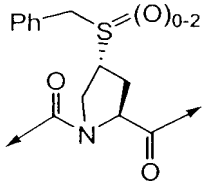

O
N
O


O
N
O

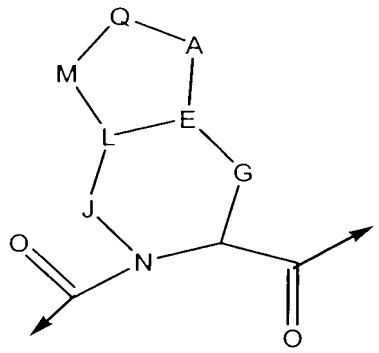

F
F
O
N
O


S
O
N
O

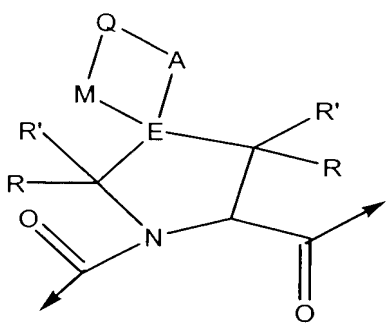

N
O
O


Ph
S
(O)0-2
O
N
O

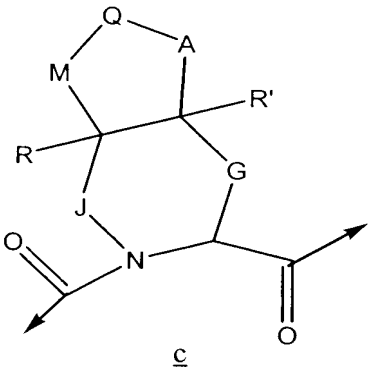
Additionally, the unit:



in Formula I may be represented by the following structures b and c:

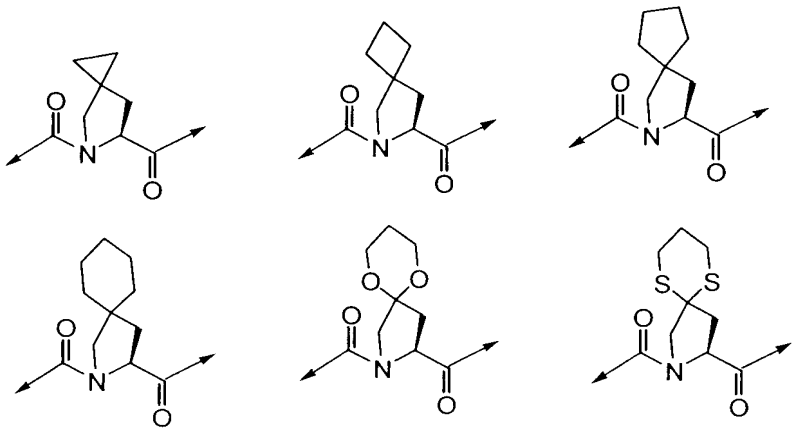


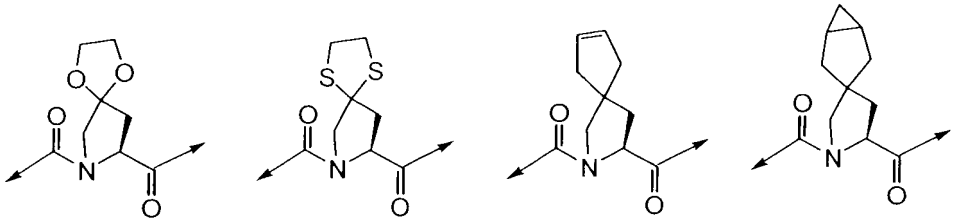
b



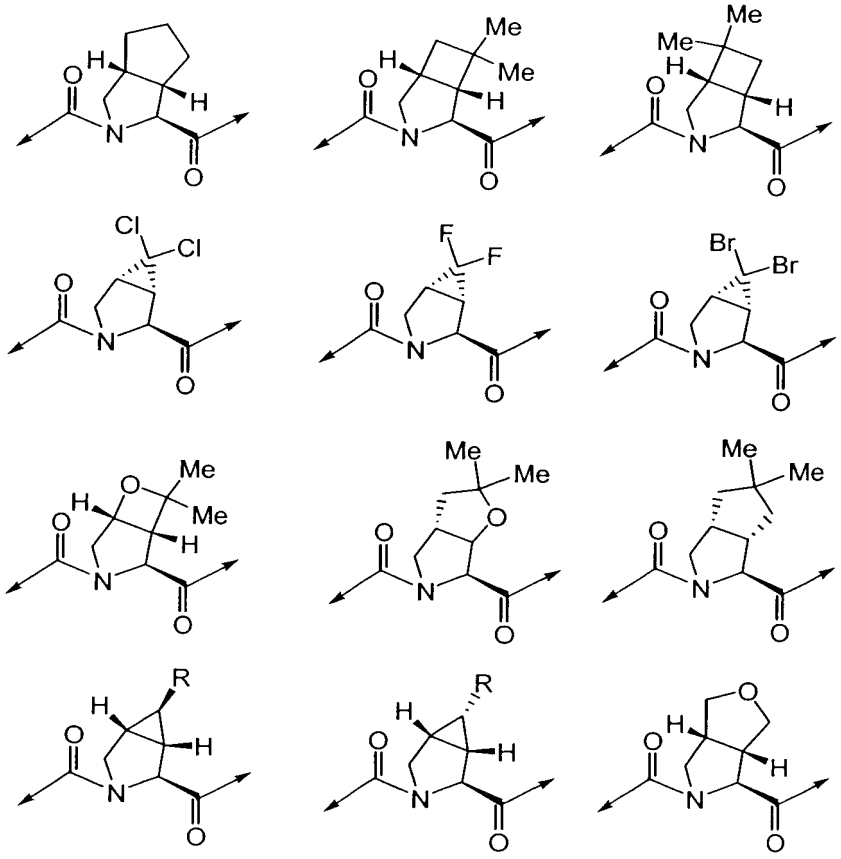
c

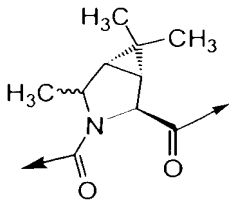
Preferred definitions for b are:

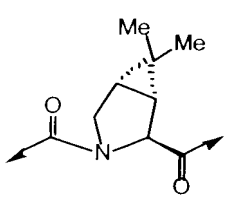


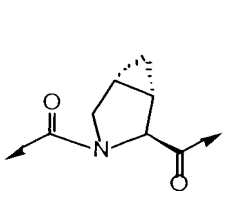


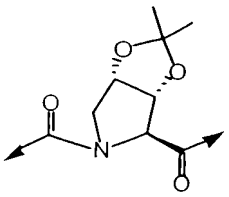
In c, G and J are independently selected from the group consisting of $(CH_2)_p$, $(CHR)_p$, $(CHR\text{-}CHR')_p$, and $(CRR')_p$; A and M are independently selected from the group consisting of O, S, SO_2, NR, $(CH_2)_p$, $(CHR)_p$, $(CHR\text{-}CHR')_p$, and $(CRR')_p$; and Q is CH_2, CHR, CRR', NH, NR, O, S, SO_2, NR, $(CH_2)_p$, $(CHR)_p$, and $(CRR')_p$. Preferred definitions for c are:

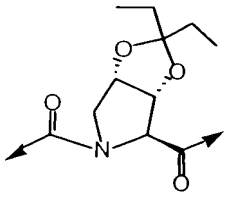


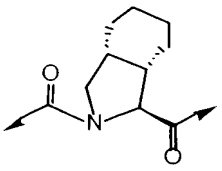


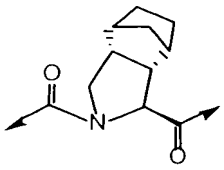


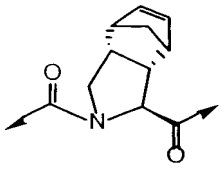


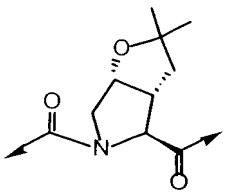


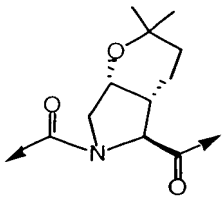


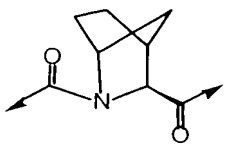


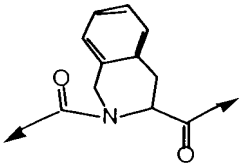


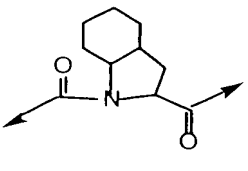


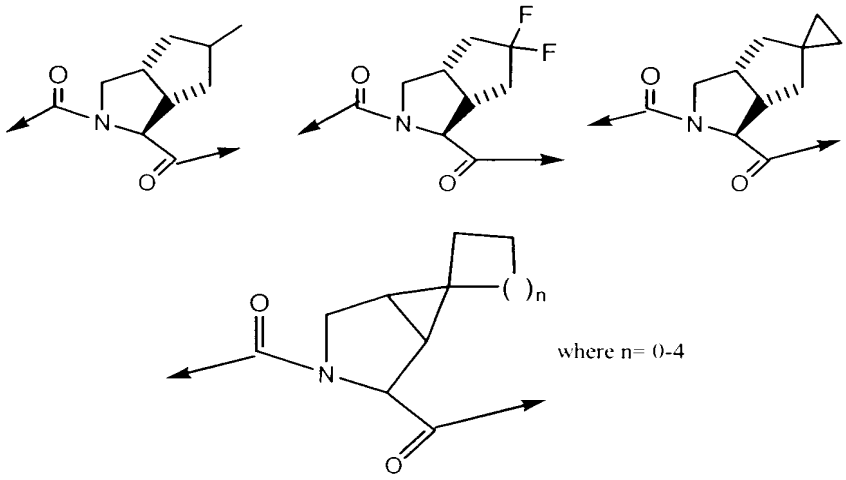




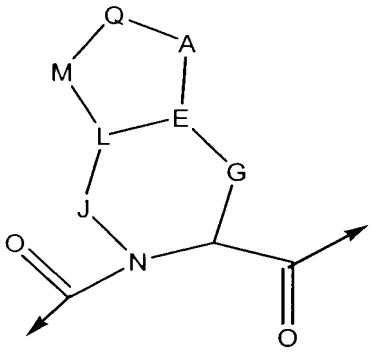




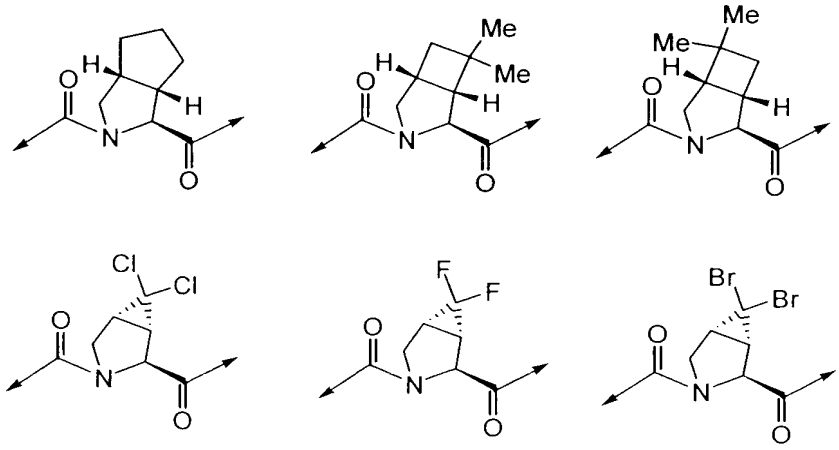


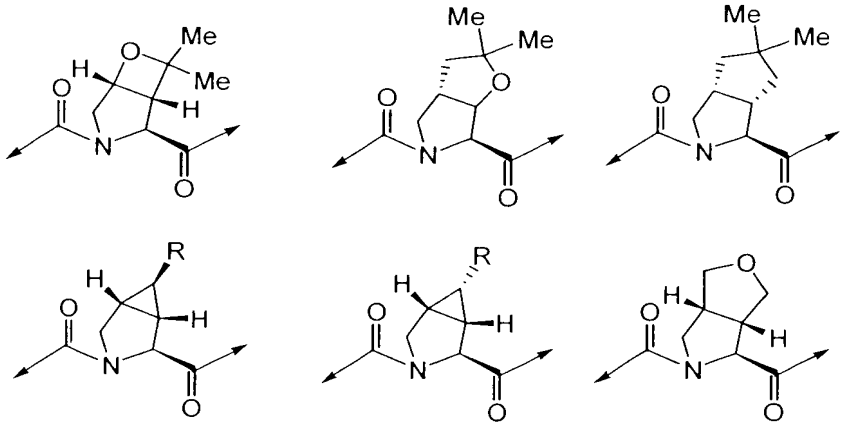


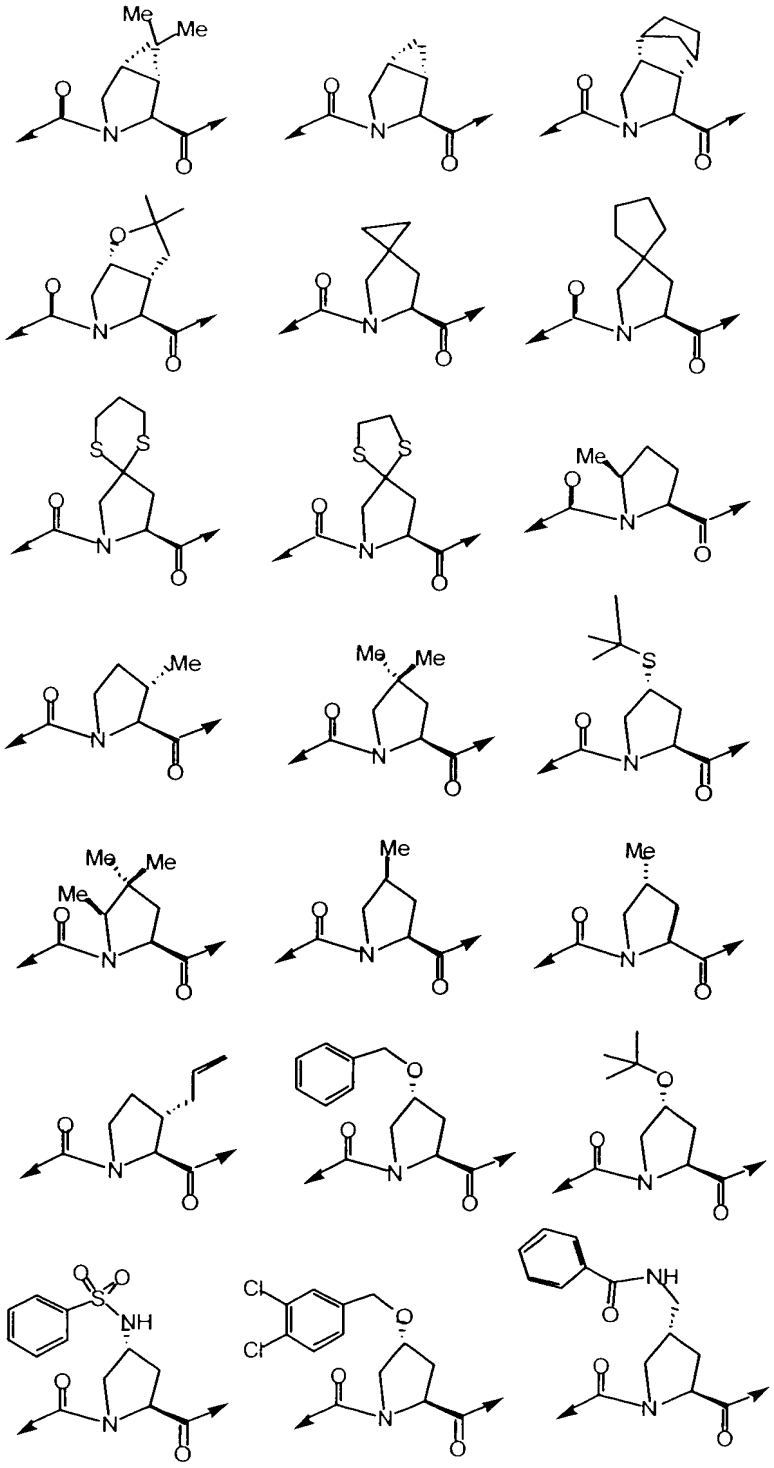
When the cyclic ring structure is depicted as:

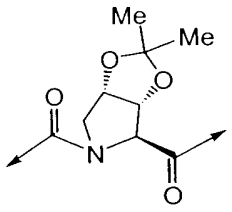


its most preferred illustrations are as follows:

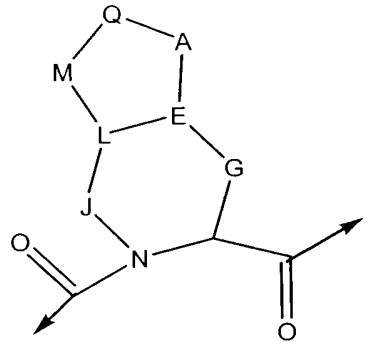



Me
Me
O
H
Me
H
O
N
O
Me
Me
O
O
N
O
Me
Me
O
N
O
R
H
H
O
N
O
R
H
H
O
N
O
O
H
H
O
N
O


Me
Me
O
N
O
S
S
NH
Cl
Cl

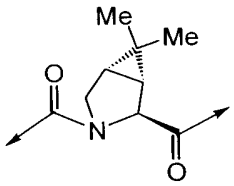


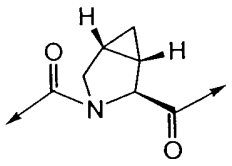
Some of the still preferred moieties for the unit:

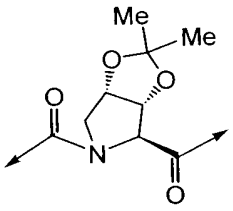


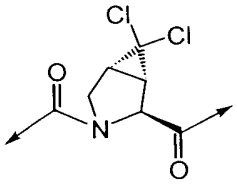
shown above, are:

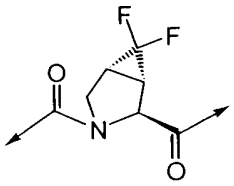
5

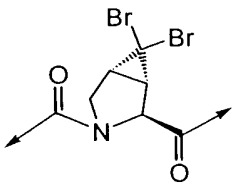


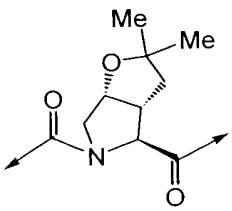


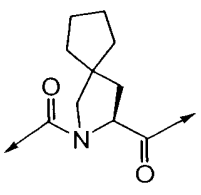


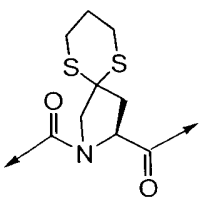


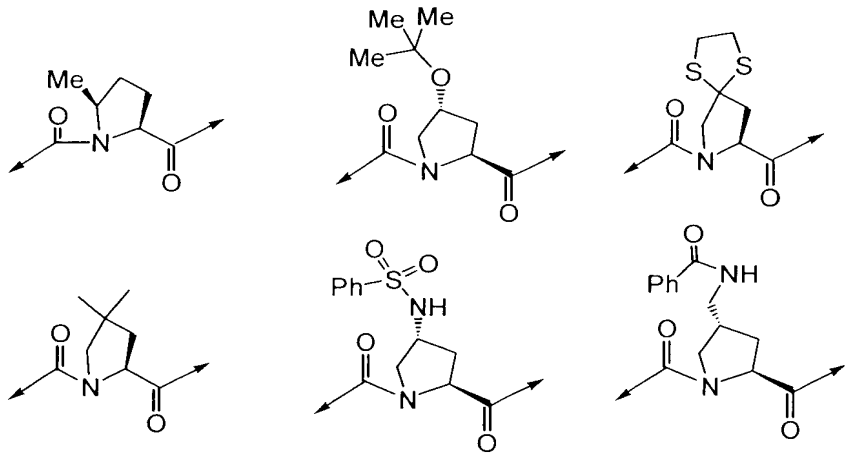












Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs. Thus, for example, the term alkyl (including the alkyl portions of alkoxy) refers to a monovalent group derived from a straight or branched chain saturated hydrocarbon by the removal of a single atom having from 1 to 8 carbon atoms, preferably from 1 to 6;

aryl – represents a carbocyclic group having from 6 to 14 carbon atoms and having at least one benzenoid ring, with all available substitutable aromatic carbon atoms of the carbocyclic group being intended as possible points of attachment. Preferred aryl groups include phenyl, 1-naphthyl, 2-naphthyl and indanyl, and especially phenyl and substituted phenyl;

aralkyl – represents a moiety containing an aryl group linked vial a lower alkyl;

alkylaryl – represents a moiety containing a lower alkyl linked via an aryl group;

cycloalkyl – represents a saturated carbocyclic ring having from 3 to 8 carbon atoms, preferably 5 or 6, optionally substituted.

heterocyclic – represents, in addition to the heteroaryl groups defined below, saturated and unsaturated cyclic organic groups having at least one O, S and/or N atom interrupting a carbocyclic ring structure that consists of one ring or

two fused rings, wherein each ring is 5-, 6- or 7-membered and may or may not have double bonds that lack delocalized pi electrons, which ring structure has from 2 to 8, preferably from 3 to 6 carbon atoms, e.g., 2- or 3-piperidinyl, 2- or 3-piperazinyl, 2- or 3-morpholinyl, or 2- or 3-thiomorpholinyl;

halogen – represents fluorine, chlorine, bromine and iodine;

heteroaryl – represents a cyclic organic group having at least one O, S and/or N atom interrupting a carbocyclic ring structure and having a sufficient number of delocalized pi electrons to provide aromatic character, with the aromatic heterocyclyl group having from 2 to 14, preferably 4 or 5 carbon atoms, e.g., 2-, 3- or 4-pyridyl, 2- or 3-furyl, 2- or 3-thienyl, 2-, 4- or 5-thiazolyl, 2- or 4-imidazolyl, 2-, 4- or 5-pyrimidinyl, 2-pyrazinyl, or 3- or 4-pyridazinyl, etc. Preferred heteroaryl groups are 2-, 3- and 4-pyridyl; such heteroaryl groups may also be optionally substituted. Additionally, unless otherwise specifically defined, as stated above, the term "substituted or unsubstituted" or "optionally substituted" refers to the subject moiety being optionally and chemically-suitably substituted with a moiety belonging to R^{12} or R^{13}. As used herein, "prodrug" means compounds that are drug precursors which, following administration to a patient, release the drug *in vivo* via some chemical or physiological process (e.g., a prodrug on being brought to the physiological pH or through enzyme action is converted to the desired drug form).

Also included in the invention are tautomers, rotamers, enantiomers and other optical isomers, as well as prodrugs, of compounds of Formula I, as well as pharmaceutically acceptable salts, solvates and derivatives thereof.

A further feature of the invention is pharmaceutical compositions containing as active ingredient a compound of Formula I (or its salt, solvate or isomers) together with a pharmaceutically acceptable carrier or excipient.

The invention also provides methods for preparing compounds of Formula I, as well as methods for treating diseases such as, for example, HCV, AIDS (Acquired Immune Deficiency Syndrome), and related disorders. The methods for treating comprise administering to a patient suffering from said disease or

diseases a therapeutically effective amount of a compound of Formula I, or pharmaceutical compositions comprising a compound of Formula I.

Also disclosed is the use of a compound of Formula I for the manufacture of a medicament for treating HCV, AIDS, and related disorders.

Also disclosed is a method of treatment of a hepatitis C virus associated disorder, comprising administering an effective amount of one or more of the inventive compounds.

Also disclosed is a method of modulating the activity of hepatitis C virus (HCV) protease, comprising contacting HCV protease with one or more inventive compounds.

Also disclosed is a method of treating, preventing, or ameliorating one or more symptoms of hepatitis C, comprising administering an effective amount of one or more of the inventive compounds. The HCV protease is the NS3 or NS4a protease. The inventive compounds inhibit such protease. They also modulate the processing of hepatitis C virus (HCV) polypeptide.

Detailed description of preferred embodiments

In one embodiment, the present invention discloses compounds of Formula I as inhibitors of HCV protease, especially the HCV NS3/NS4a serine protease, or a pharmaceutically acceptable derivative thereof, where the various definitions are given above.

Representative compounds of the invention which exhibit excellent HCV protease inhibitory activity are listed below in **Tables 1 to 5** along with their activity (ranges of Ki* values in nanomolar, nM). Several compounds as well as addiitonal compounds are additionally disclosed in the Claims.

Table 1: Compounds and HCV protease continuous assay results

Compound from Example No.	Ki* Range
1	C
2	C
3	C
4	C
5	C
6	C
7	C
8	C
9	C
10	C
11	C
12	C
13	C
14	C
15	C
16	C
17	C
18	C
19	C
20	C
21	C
22	C
23	C
24	C
25	C
26	C
27	C
28	C
29	C
30	C
31	C
32	C
33	C
34	C
35	C
36	C
37	C

38	C
39	C
40	C
41	C
42	C
43	C
44	C
45	C
46	C
47	C
48	C
49	C
50	C
51	C
52	C
53	C
54	C
55	C
56	C
57	C
58	C
59	C
60	C
61	C
62	C
63	C
64	C
65	C
66	C
67	C
68	B
69	C
70	C
71	B
72	C
73	B
74	C
75	C
76	A
77	B
78	A
79	C
80	A
81	C

82	A
83	B
84	C
85	C
86	B
87	B
88	A
89	B
90	C
91	C
92	C
93	C
94	C
95	C
96	C
97	C
98	B
99	B
100	A
101	A
102	C
103	C
104	C
105	C
106	C
107	B
108	A
109	A
110	A
111	A
112	A
113	B
114	A
115	B
116	A
117	A
118	A
119	A
120	A
121	B
122	B
123	A
124	B
125	B

126	B
127	A
128	A
129	A
130	B
131	A
132	A
133	A
134	B
135	A
136	A
137	A
138	A
139	A
140	B
141	A
142	A
143	B
144	B
145	C
146	A
147	A
148	B
149	A
150	A
151	A
152	A
153	A
154	A
155	B
156	B
157	B
158	C
159	B
160	A
161	A
162	A
163	C
164	A
165	C
166	B
167	A
168	C
169	B

170	B
171	A
172	A
173	A
174	A
175	A
176	B
177	B
178	A
179	A
180	B
181	A
182	B
183	A
184	A
185	A
186	A
187	A
188	A
189	B
190	B
191	B
192	A
193	A
194	B
195	A
196	B
197	A
198	A
199	A
200	A
201	B
202	A
203	B
204	B
205	B
206	B
207	B
208	A
209	A
210	A
211	A
212	A
213	B

214	B
215	B
216	B
217	C
218	A
219	A
220	A
221	A
222	A
223	B
224	C
225	C
226	A
227	A
228	C
229	A
230	A
231	A
232	C
233	C
234	C
235	C
236	B
237	C
238	A
239	C
240	A
241	C
242	B
243	C
244	B
245	C
246	B
247	A
248	A
249	C
250	C
251	B
252	C
253	C
254	B
255	B
256	A
257	C

258	A
259	A
260	C
261	C
262	A
263	B
264	B
265	C
266	B
267	A
268	C
269	A
270	C
271	A
272	C
273	C
274	C
275	C
276	A
277	B
278	A
279	B
280	A
281	C
282	C
283	C
284	C
285	C
286	C
287	C
288	B
289	B
290	C
291	C
292	C
293	C
294	C
295	C
296	B
297	C
298	C
299	B
300	B
301	C

302	C
303	B
304	C
305	C
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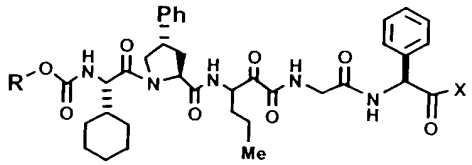
309	C
310	C
311	C
312	C
313	B
314	A
315	B
316	B
317	A
318	A
319	A
320	A
321	C
322	C
323	C
324	C
325	A
326	A
327	C
328	B
329	B
330	A
331	A
332	A
333	B
334	B
335	B
336	A
337	A
338	C
339	A
340	C
341	C
342	C
343	A
344	C
345	C

346	C
347	B
348	B
349	C
350	C
351	C
352	C
353	C
354	C
355	C
356	A
357	A
358	C
359	A
360	B
361	B
362	C

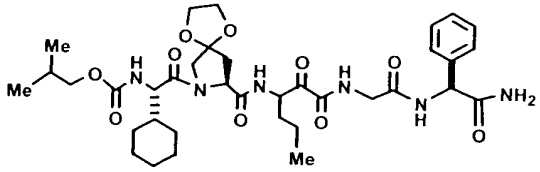
HCV continuous assay Ki* range:

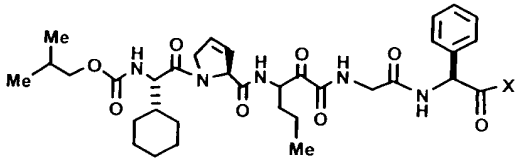
Category A = 1-100 nM; Category B = 101-1,000 nM; Category C >1000 nM.

Some of the types of the inventive compounds and methods of synthesizing the various types of the inventive compounds of Formula I are listed below, then schematically described, followed by the illustrative Examples.

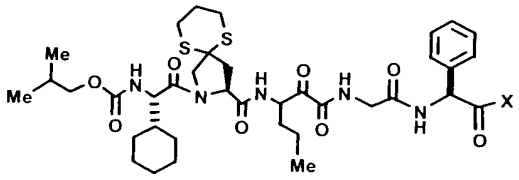


(R = t-butyl, X = NH_2)
(R = Isobutyl, X = NH_2)
(R = t-butyl, X = OH)
(R = Trichloroethyl, X = OH)

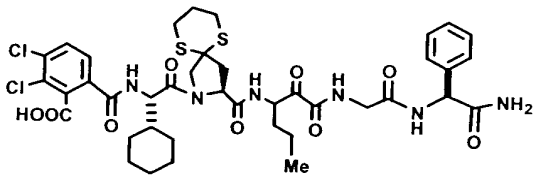


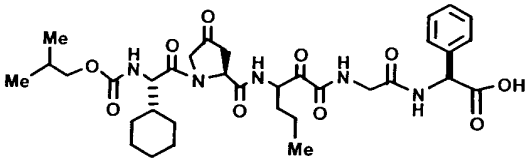


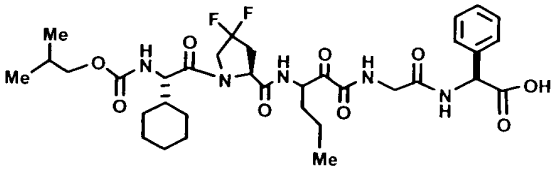
(X = O^{t}Bu)
(X = OH)

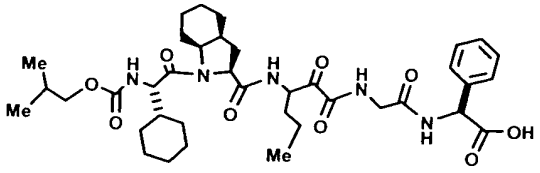


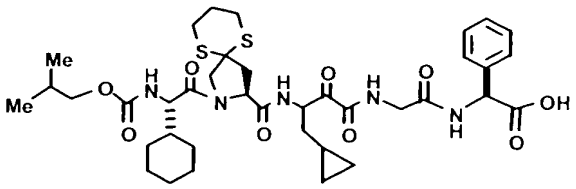
(X = OH)
(X = O^{t}Bu)
(X = NH_2)
(X = NHMe)
(X = NMe_2)

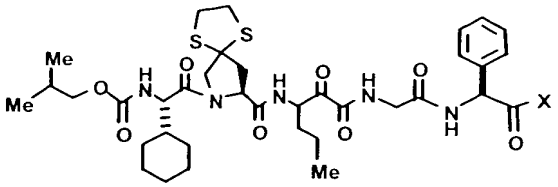




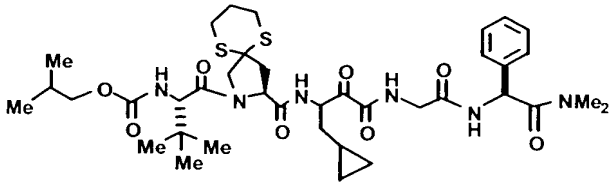


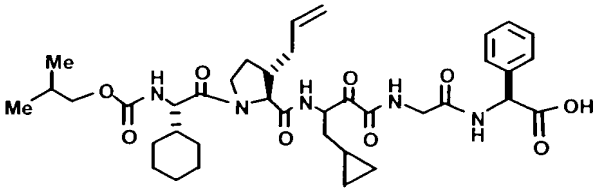


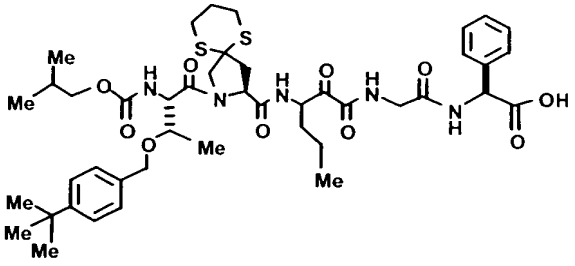


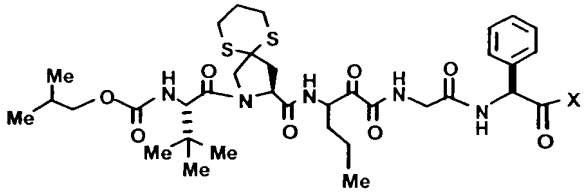


(X = NH_2)
(X = NMe_2)
(X = NHMe)
(X = OH)

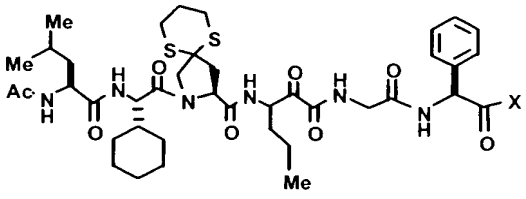




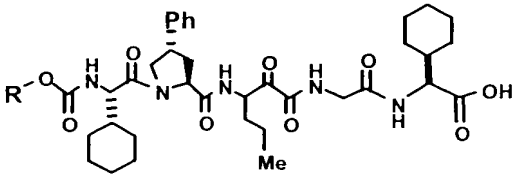




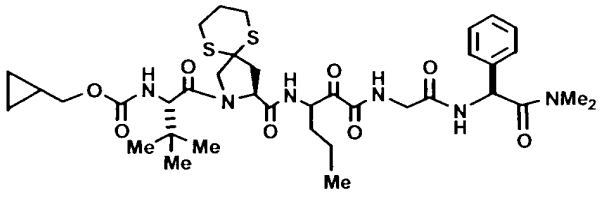
(X = O^{t}Bu)
(X = OH)
(X = NH_2)
(X = NMe_2)

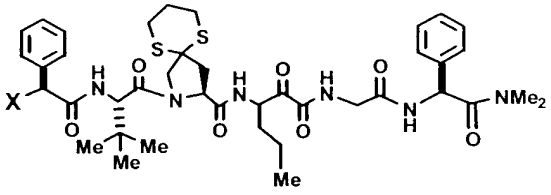


(X = O^{t}Bu)
(X = OH)
(X = NH_2)
(X = NMe_2)
(X = NMeOMe)

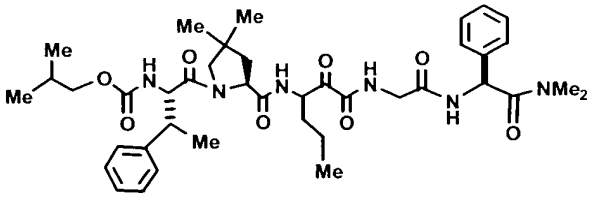


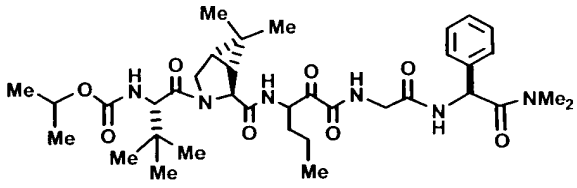
(R = t-butyl)
(R = Isobutyl)

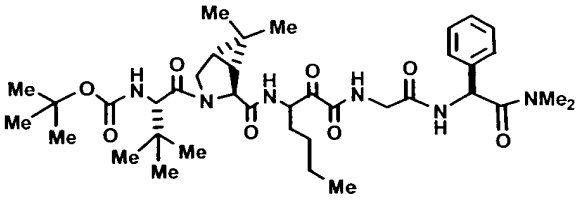


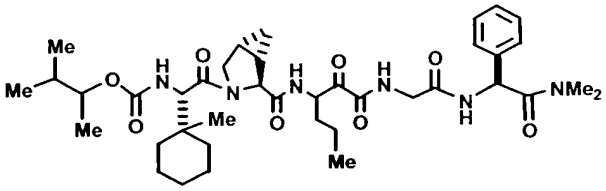


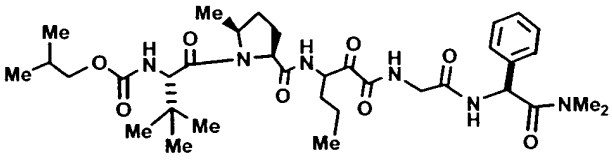
(X = Me, Y = CH_2Me)
(X = OAc, Y = Me)

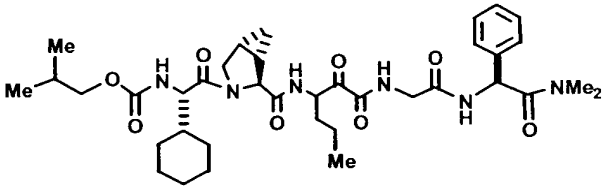


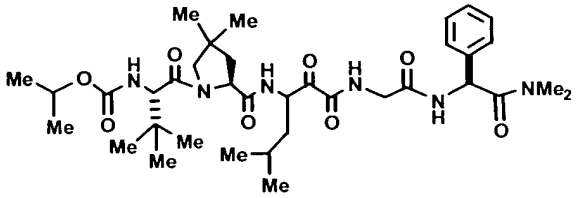


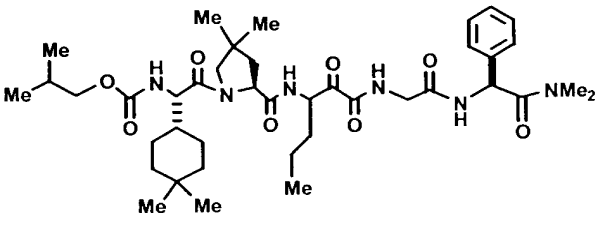


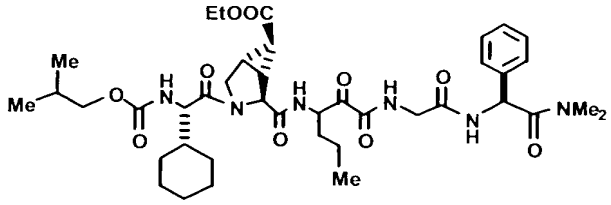


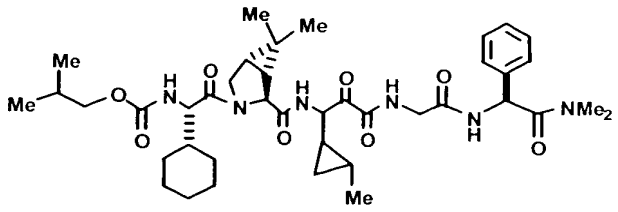


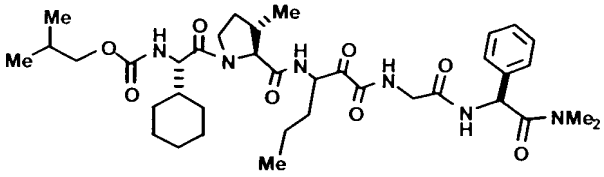


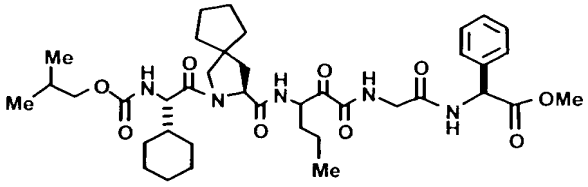


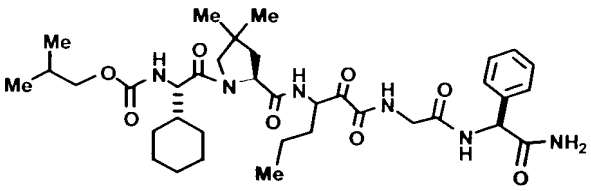


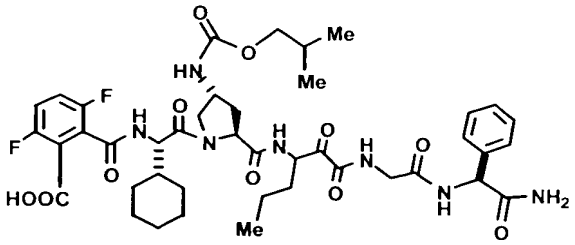


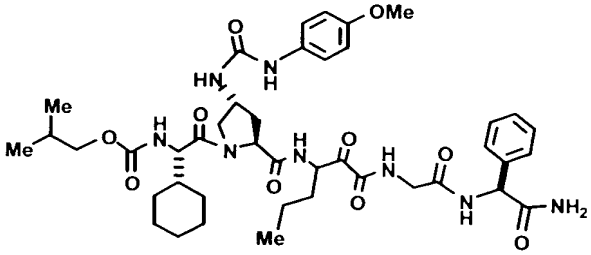


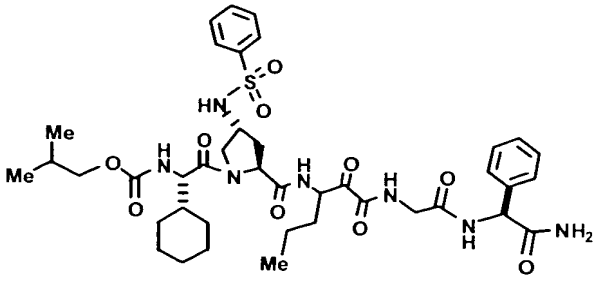


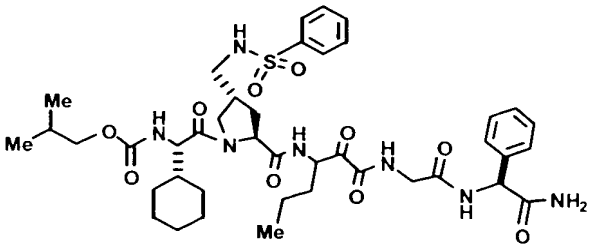


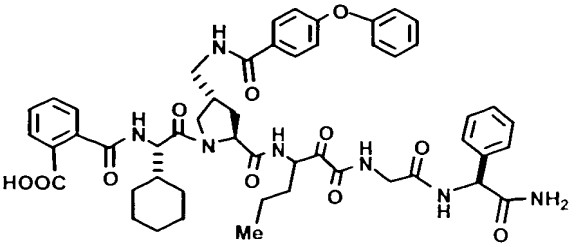


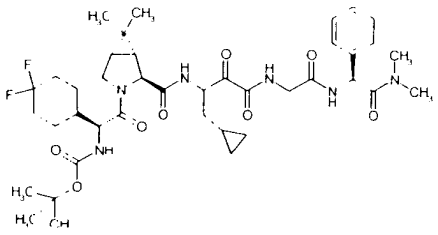


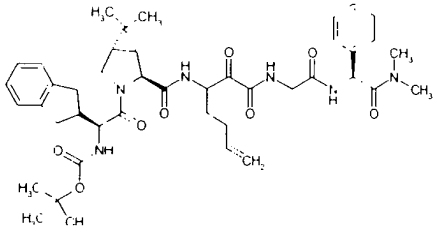


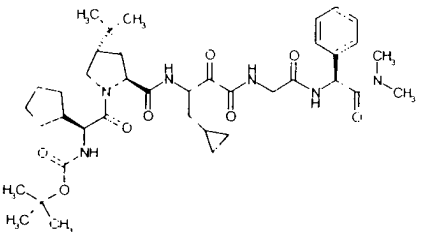


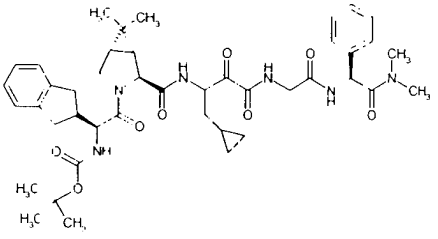


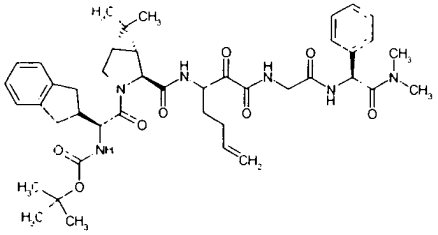


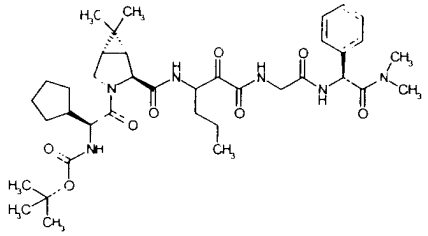


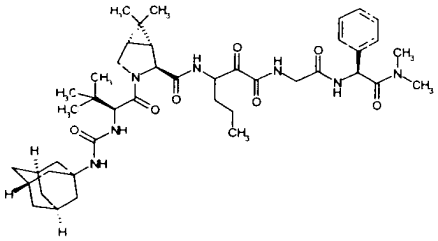


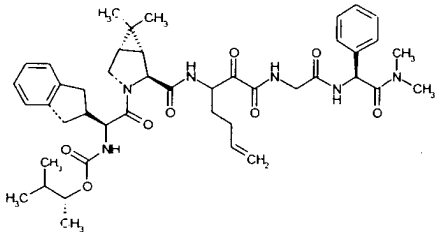


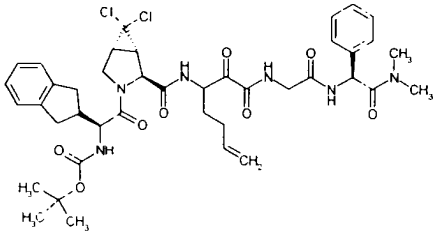


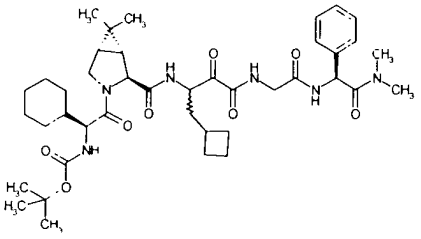


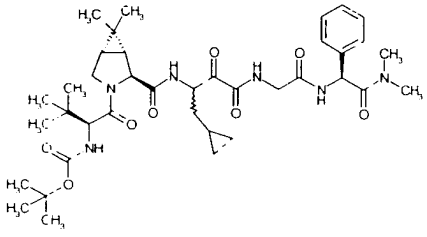


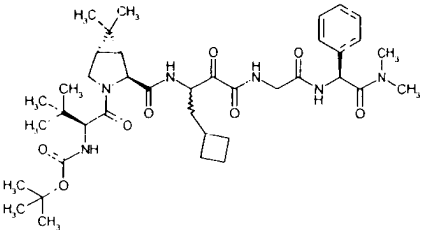


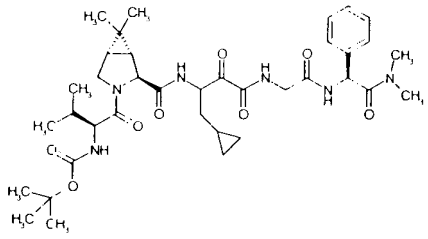


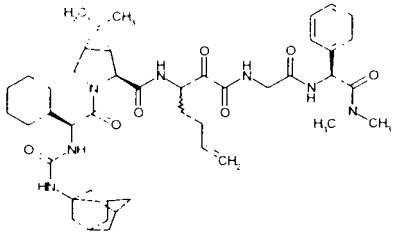


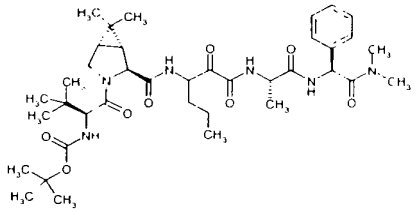


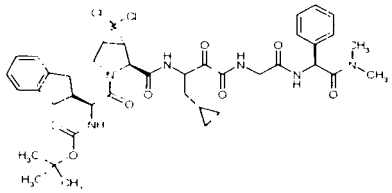


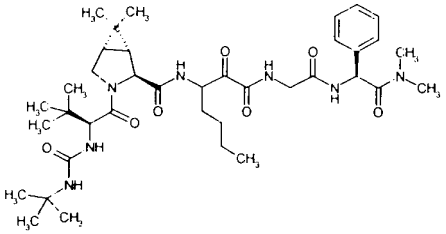


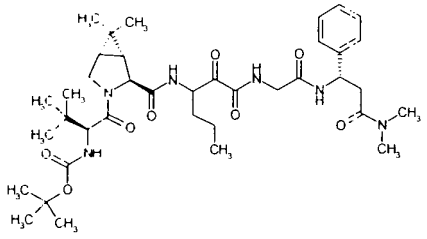


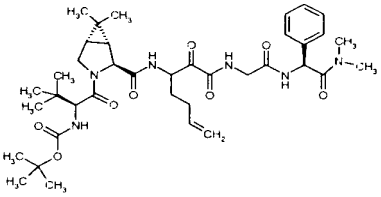


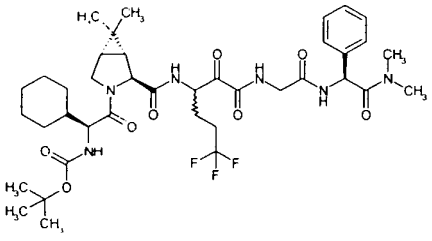


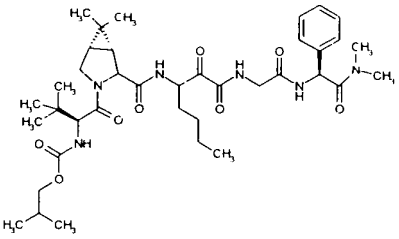


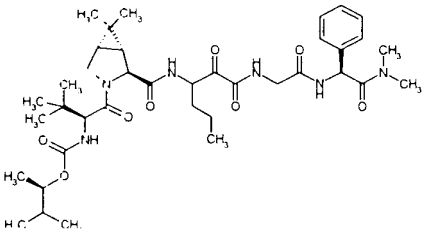


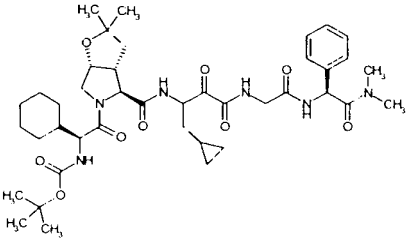


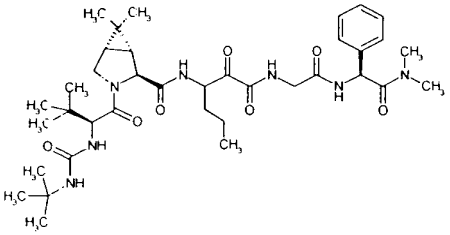


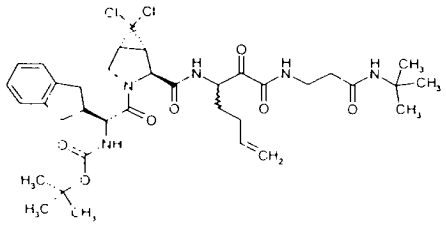


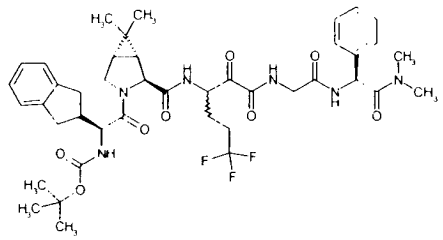


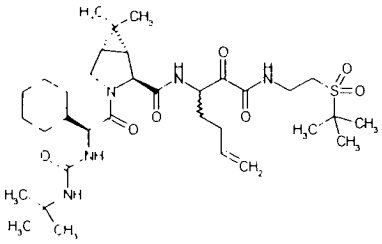


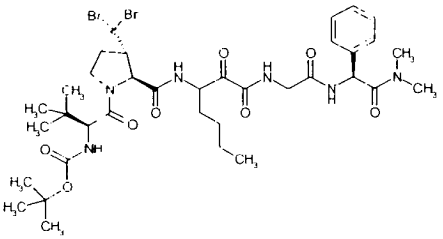


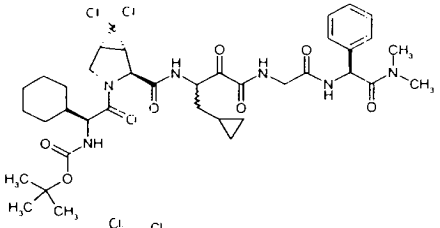


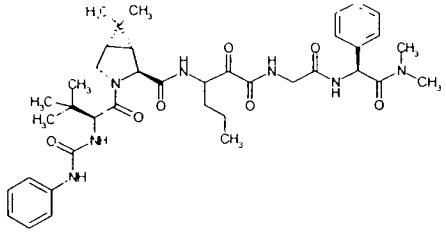


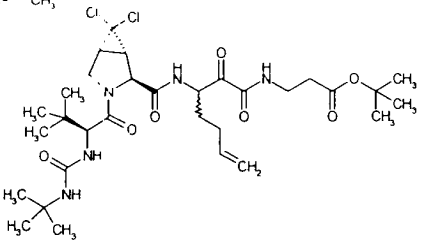


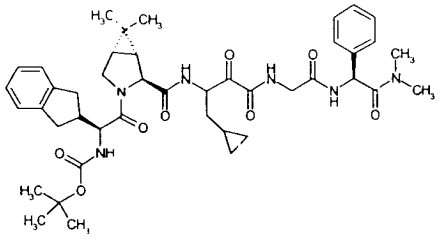


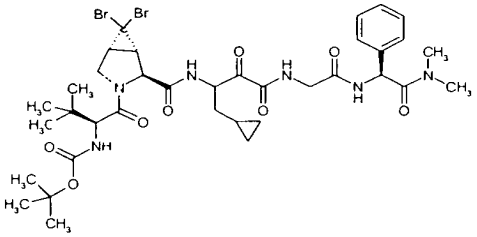


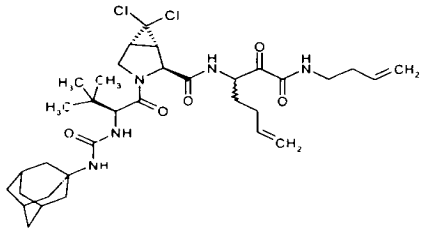


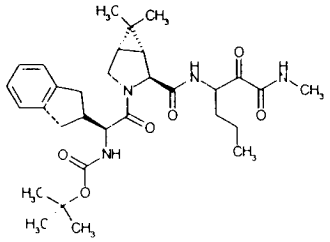


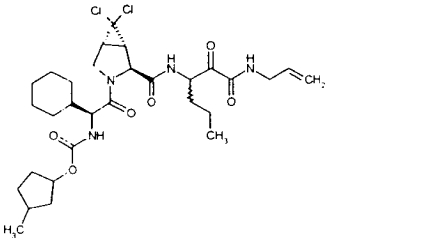


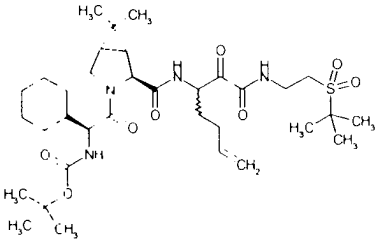


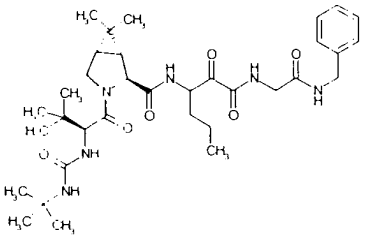


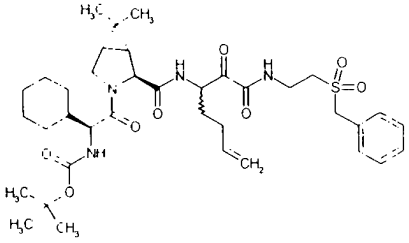


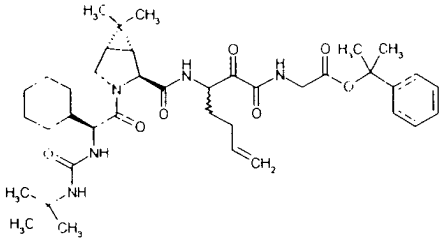


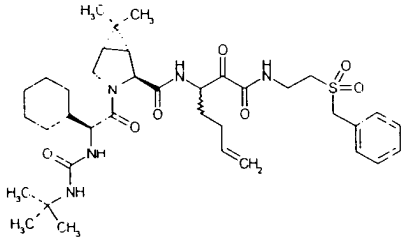


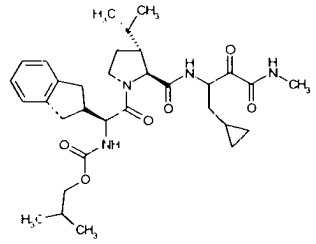


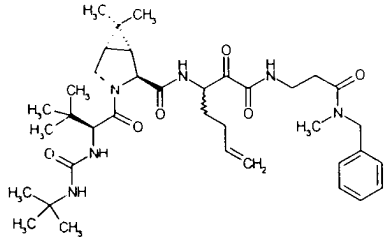


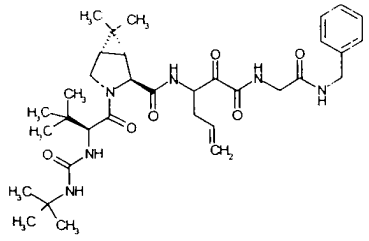


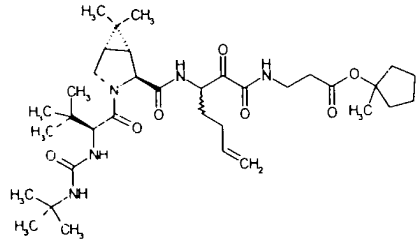


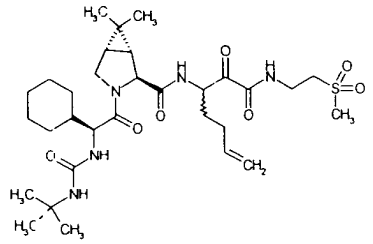


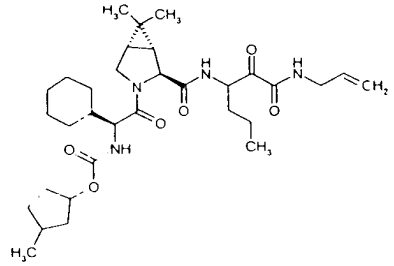


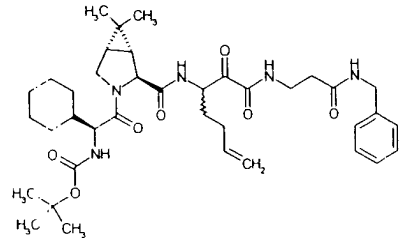


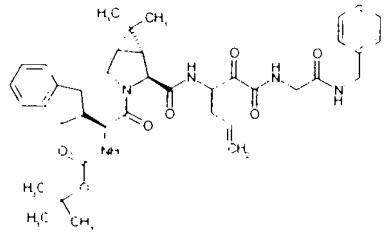


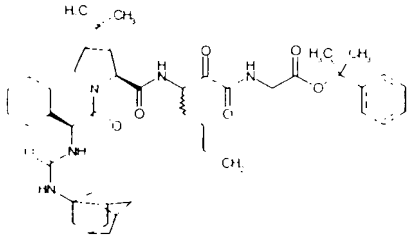


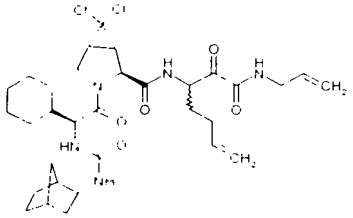


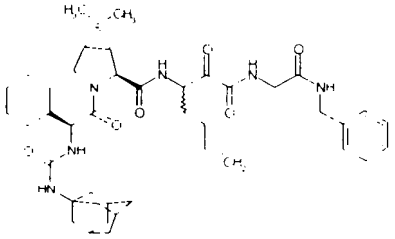


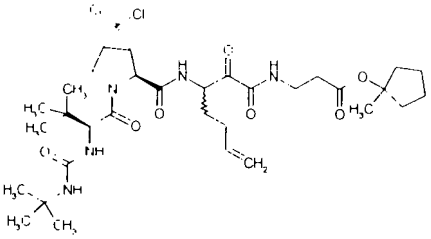


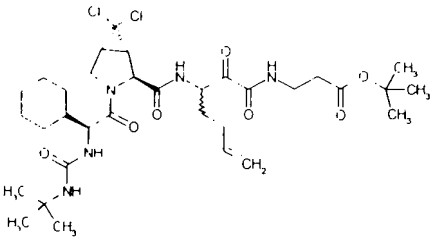


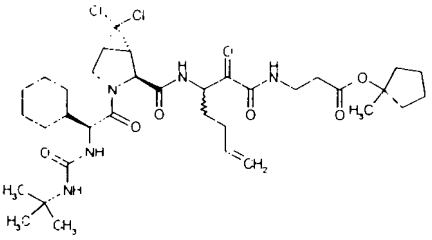


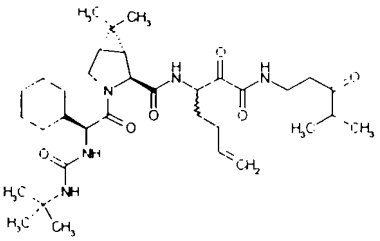


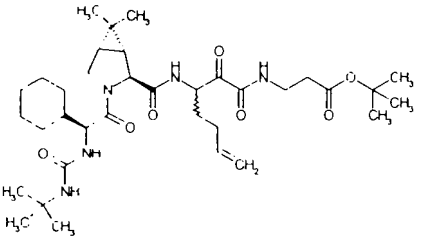


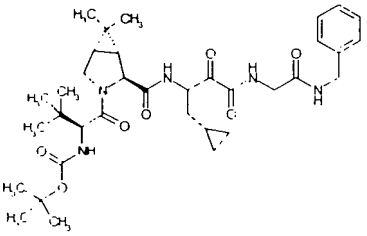


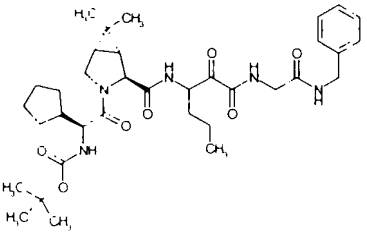


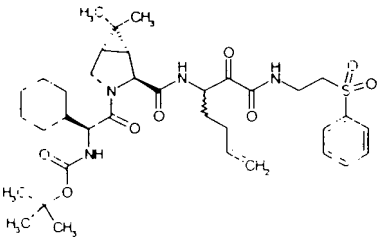


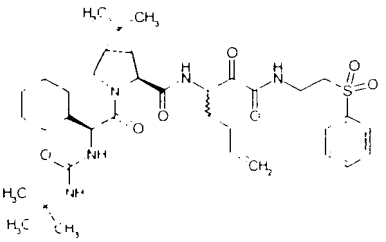


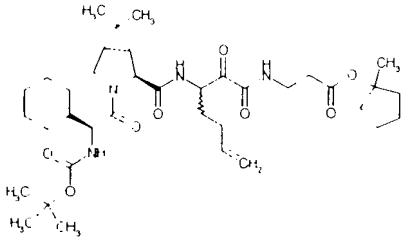


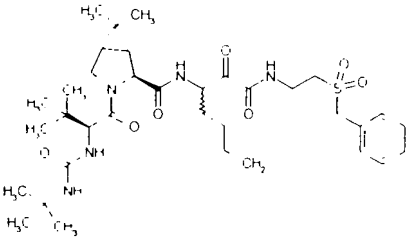


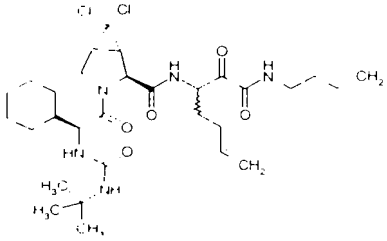


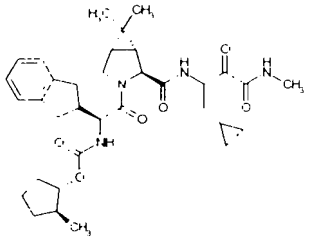


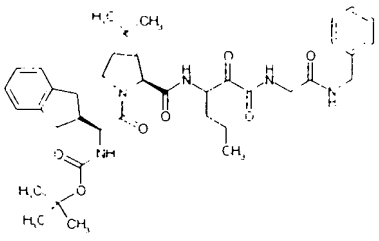


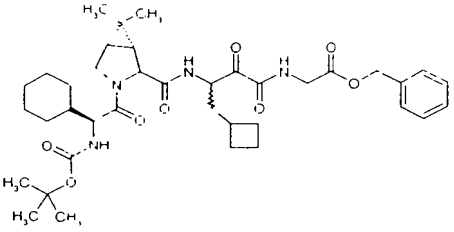


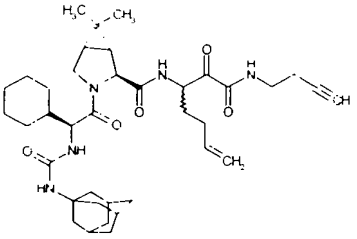


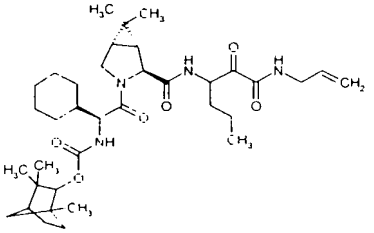


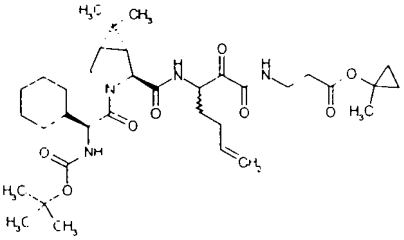


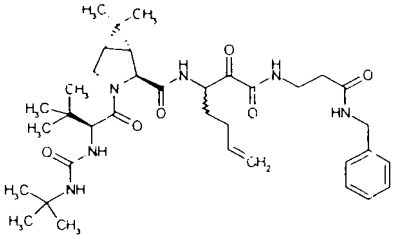


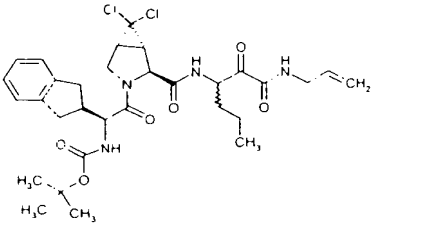


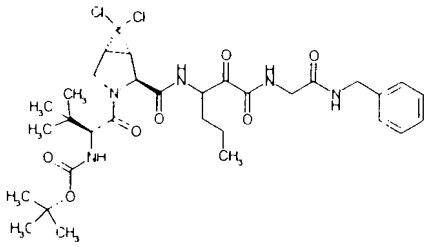


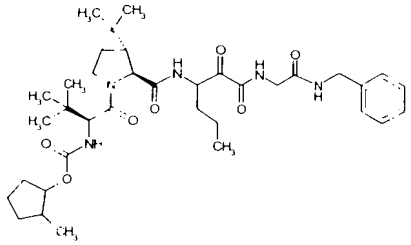


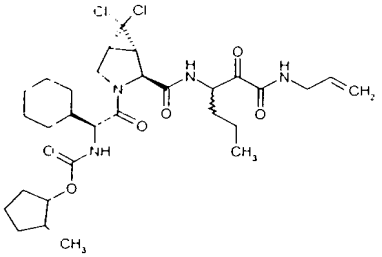


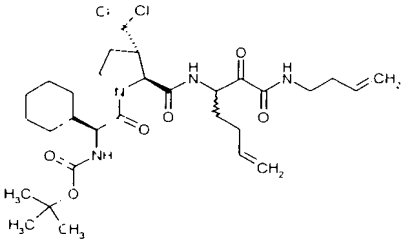


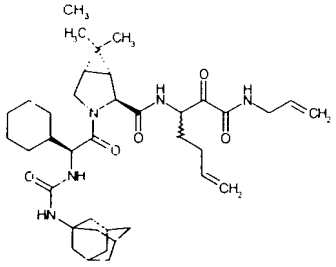


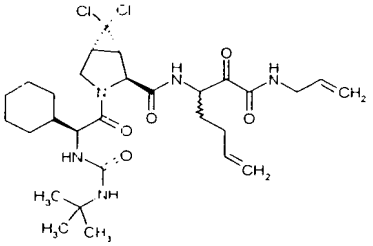


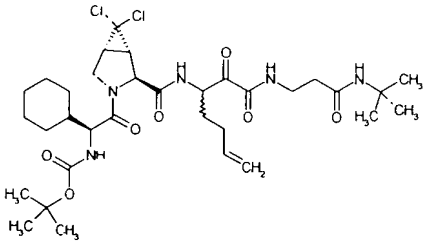


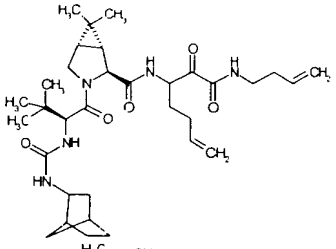


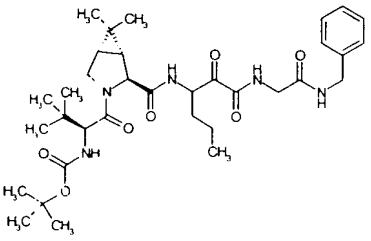


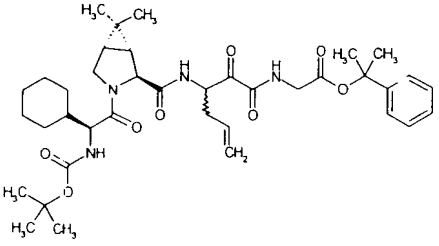


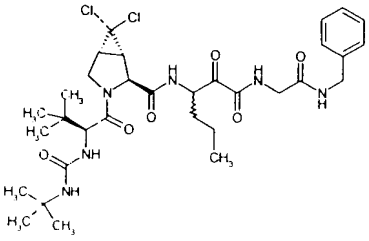


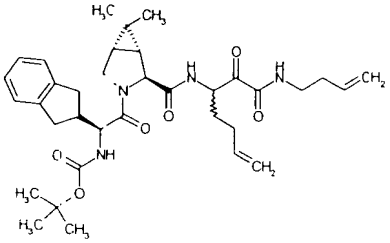


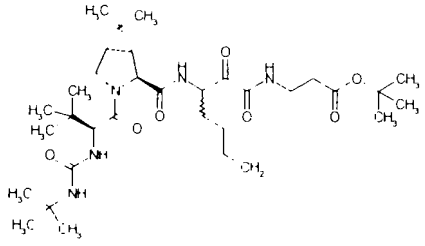


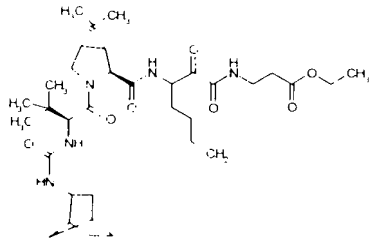


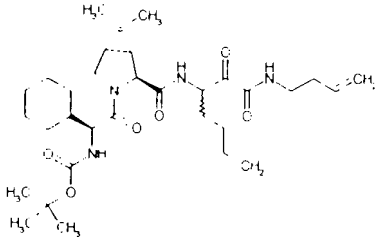


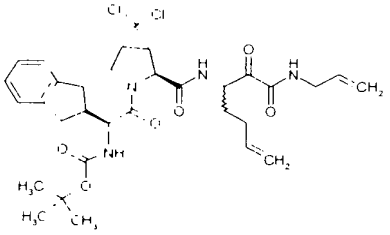


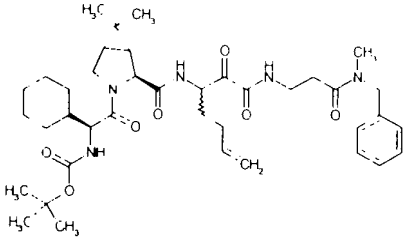


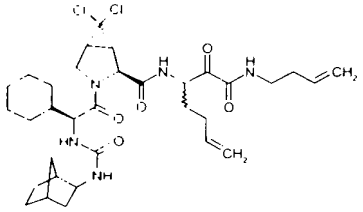


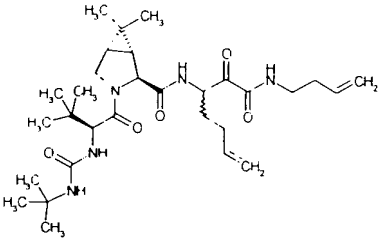


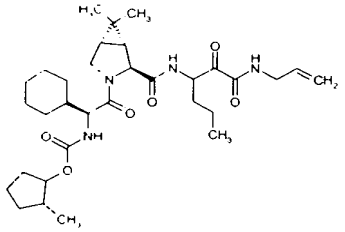


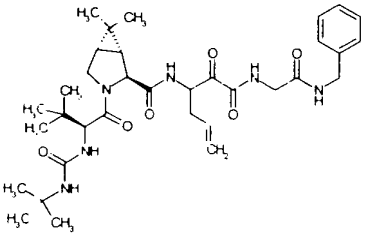


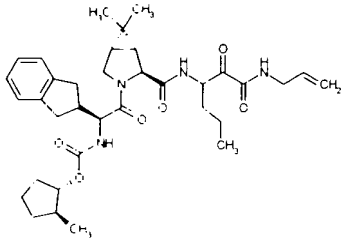


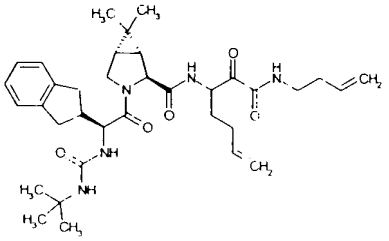


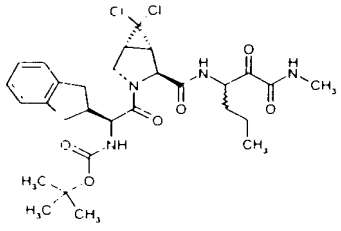


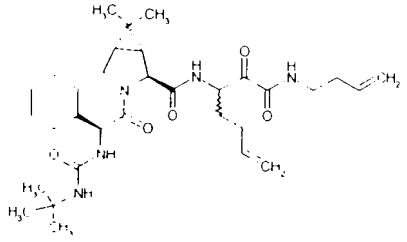


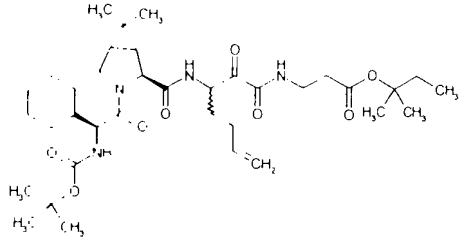


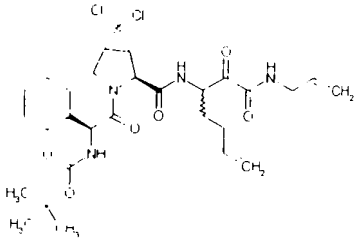


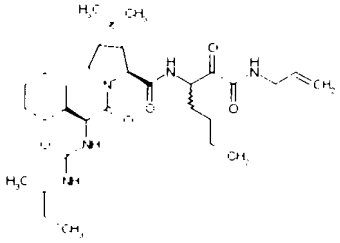


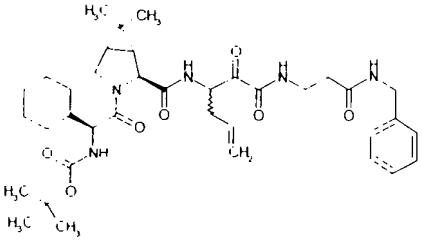


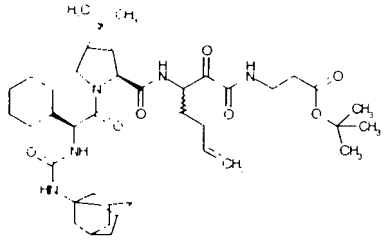


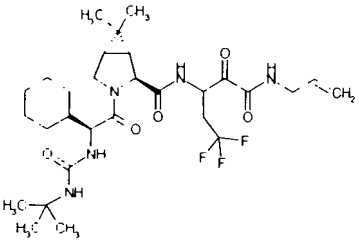


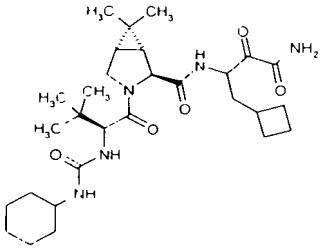


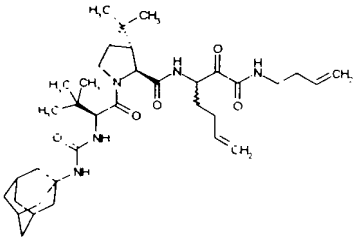


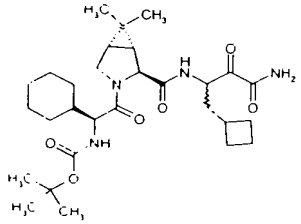


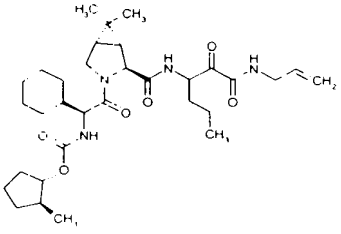


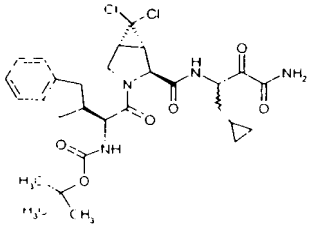


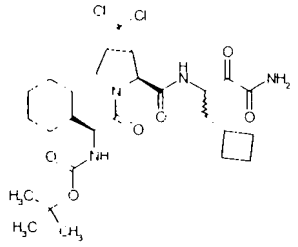


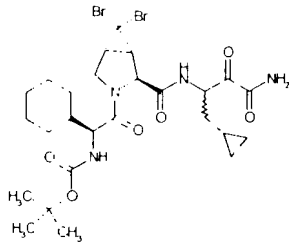


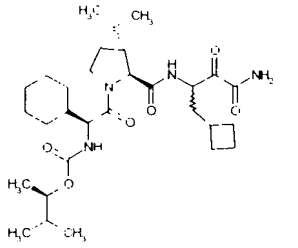


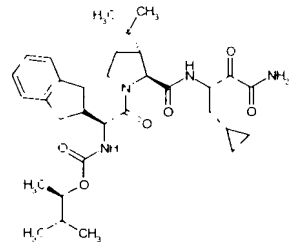


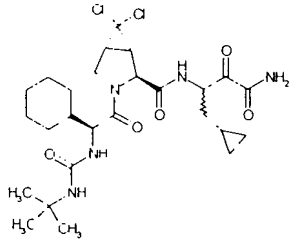


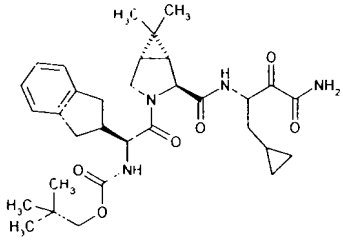


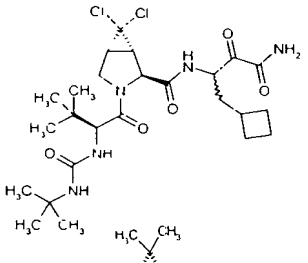


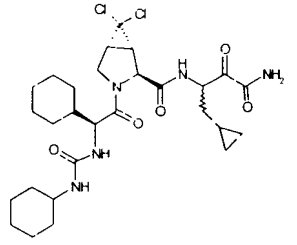


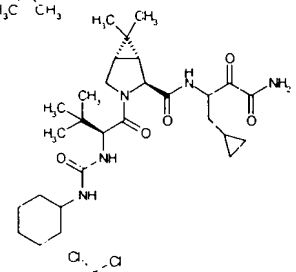


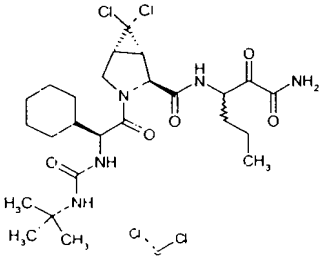


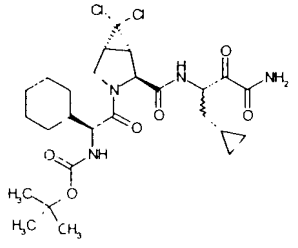


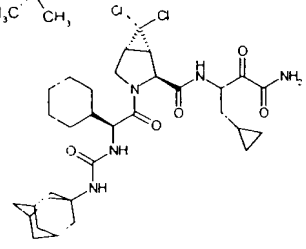












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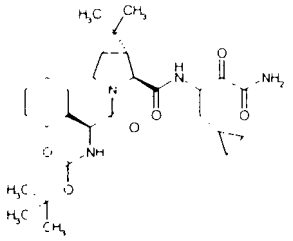

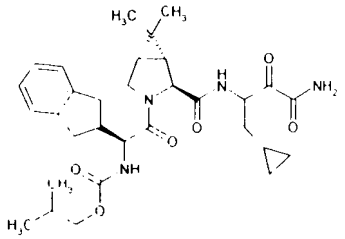

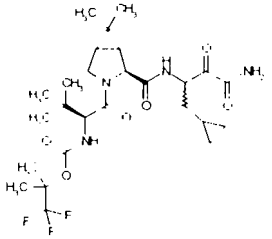

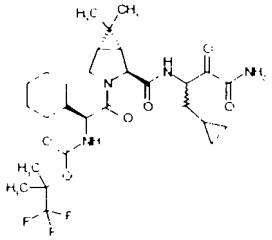

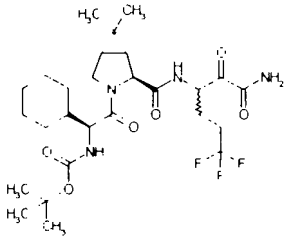

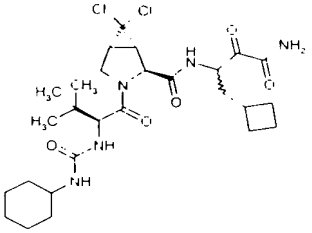

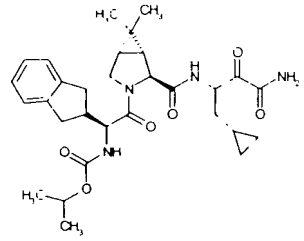

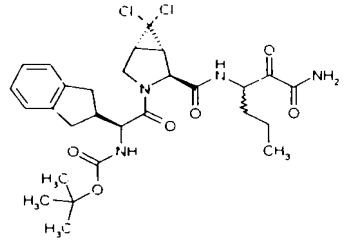

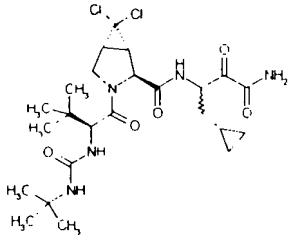

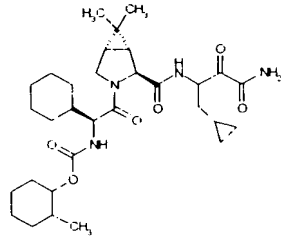

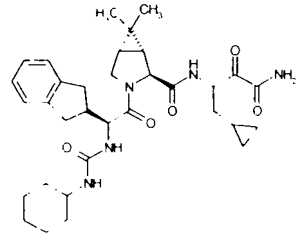

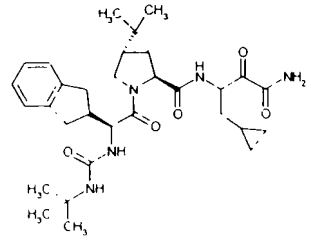

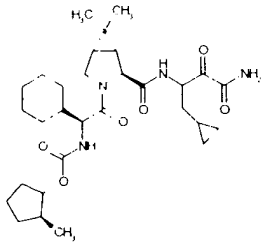

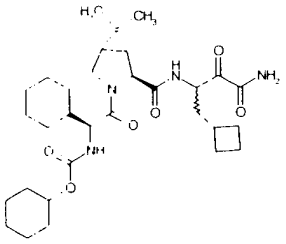

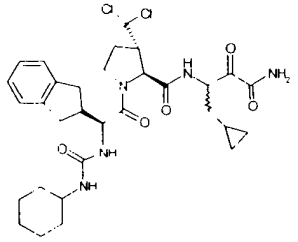

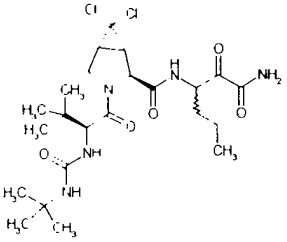

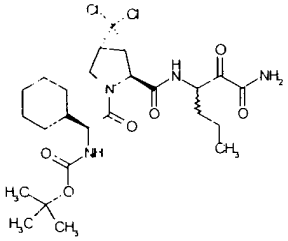

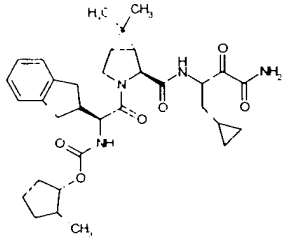

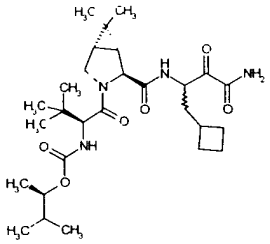

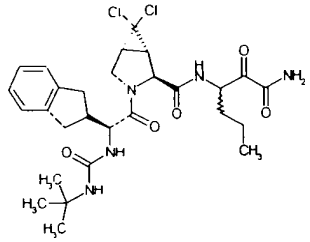

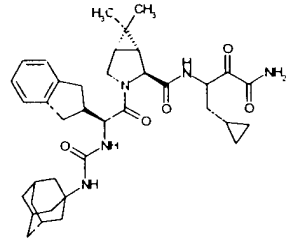

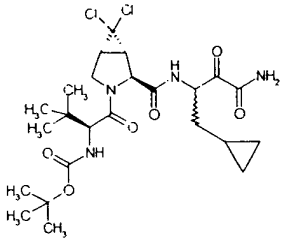

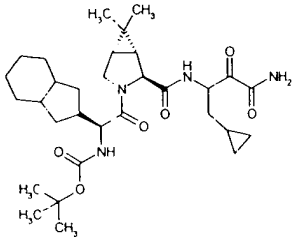

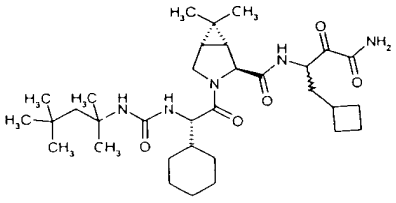

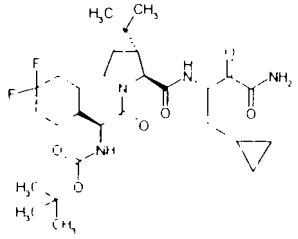

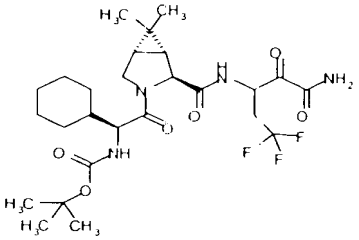

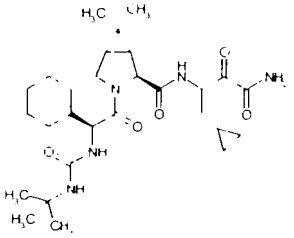

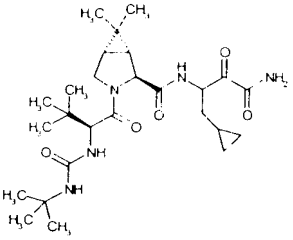

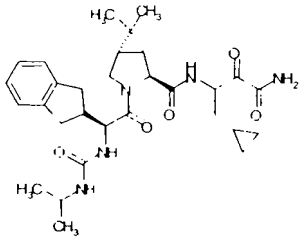

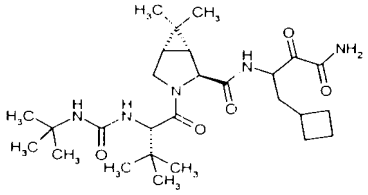

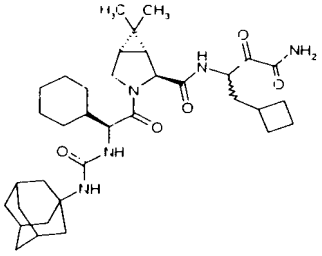

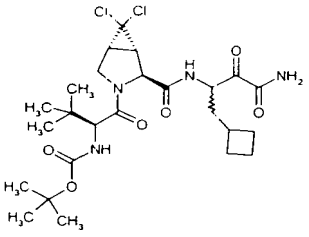

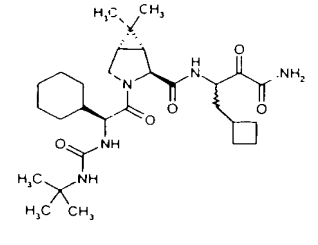

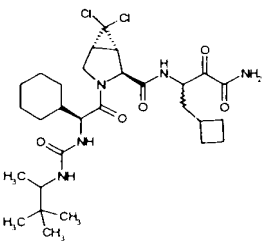

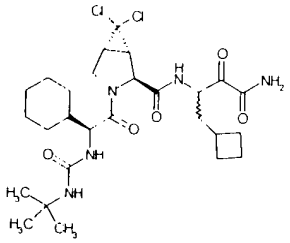

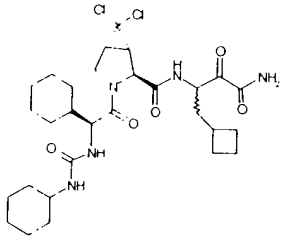

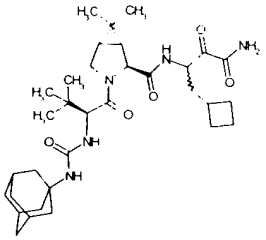

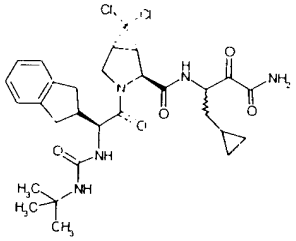

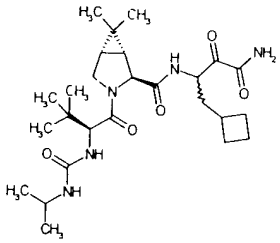

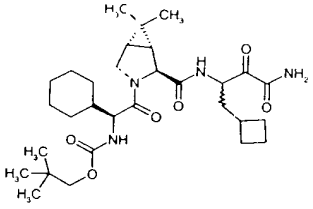

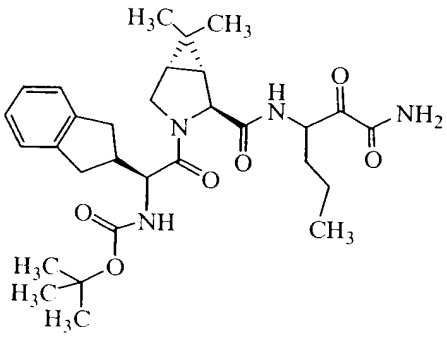

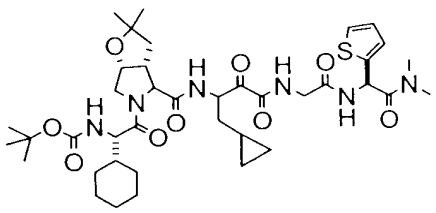

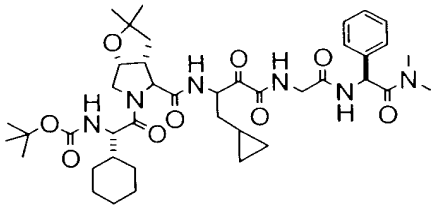

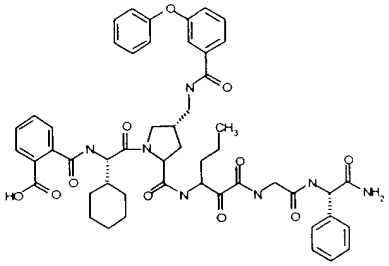

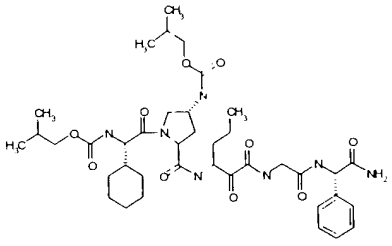

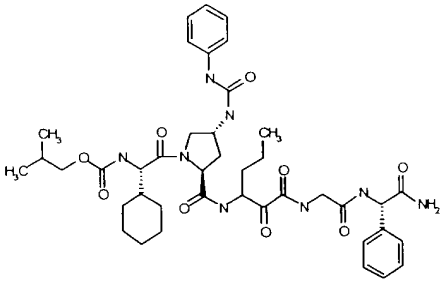

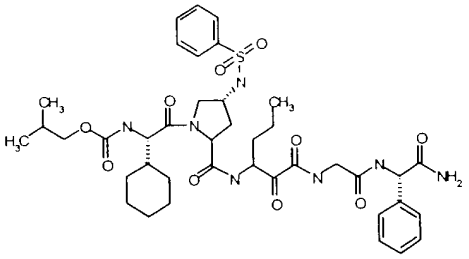

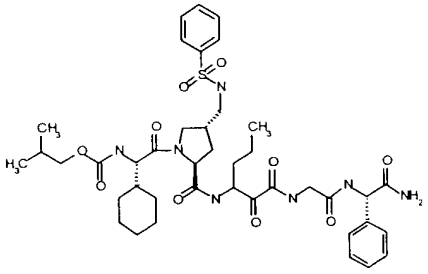

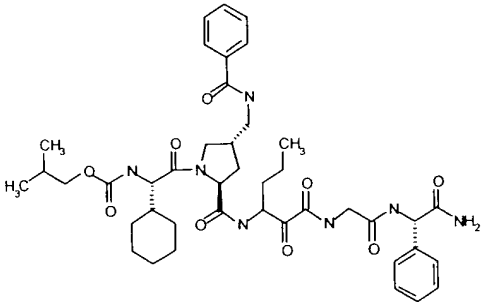

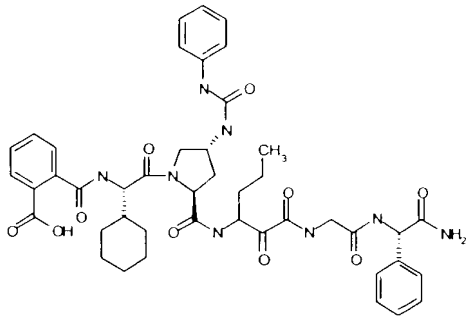

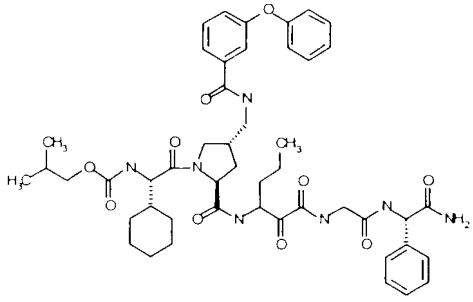

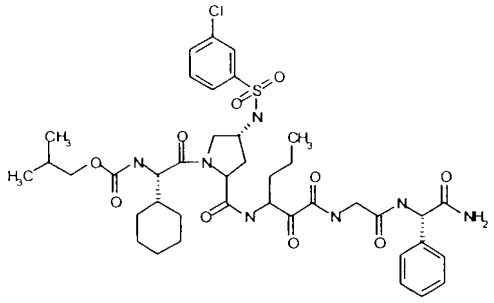

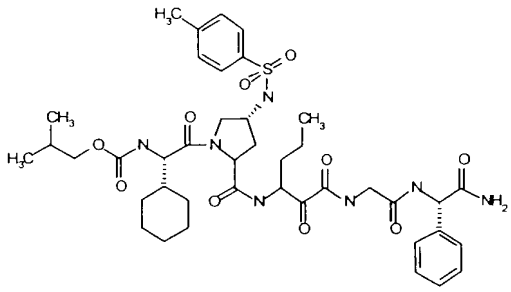

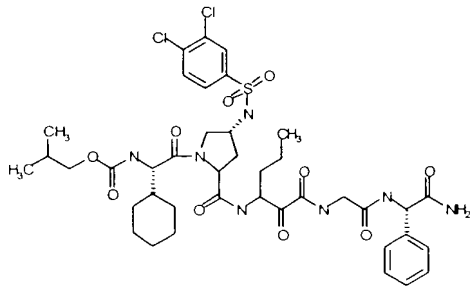

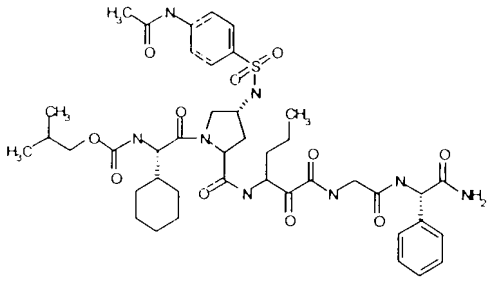

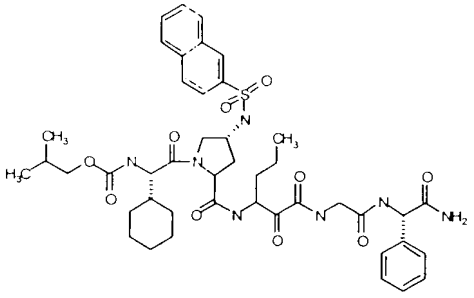

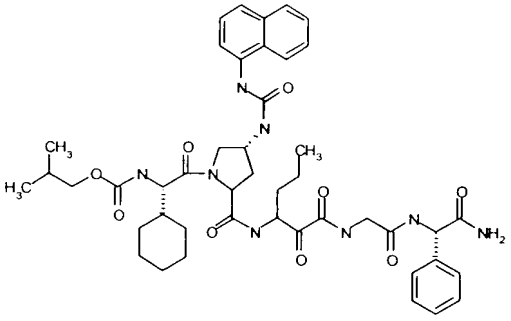

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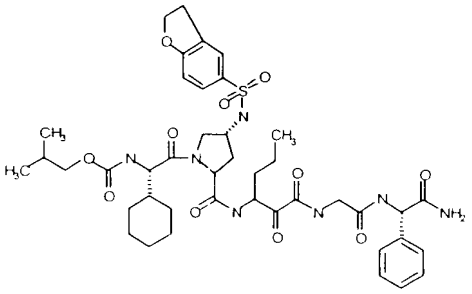

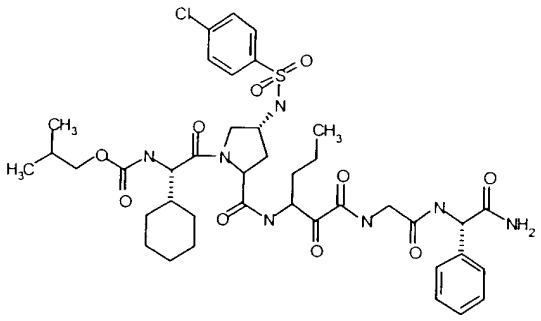

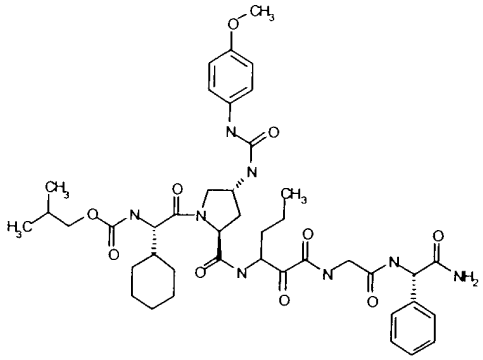

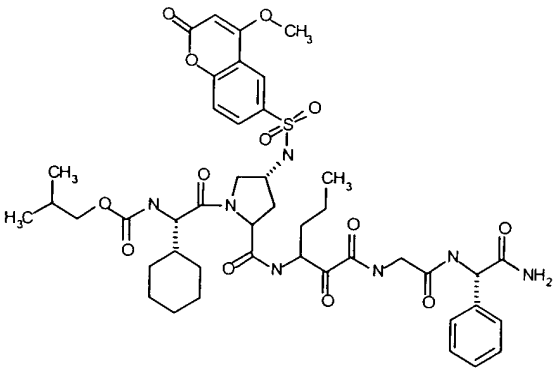

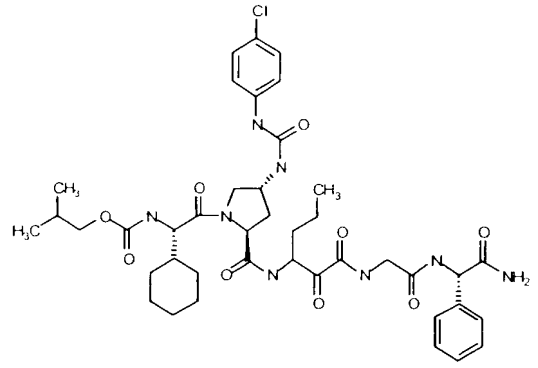

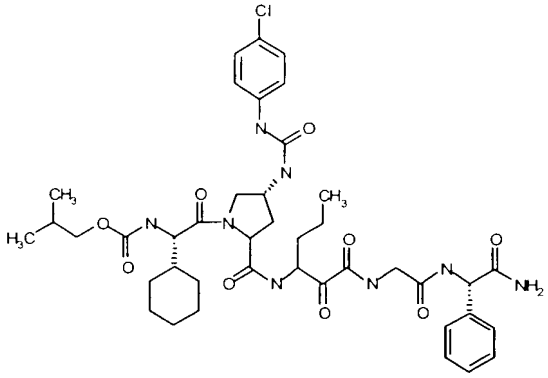

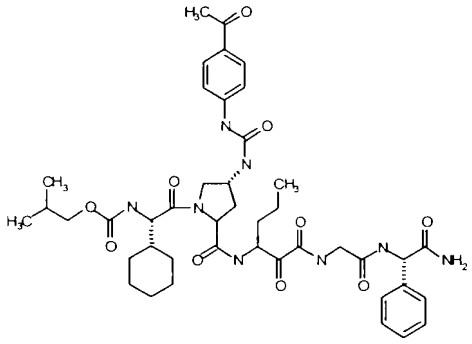

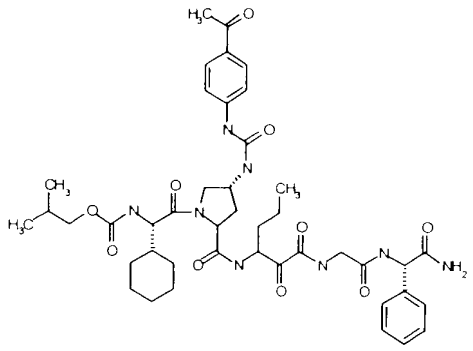

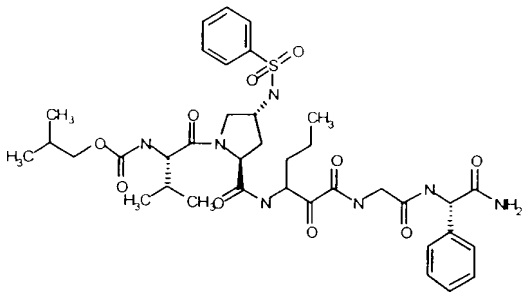

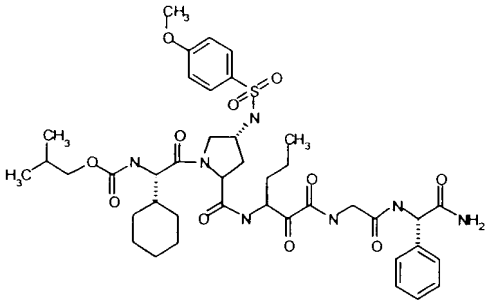

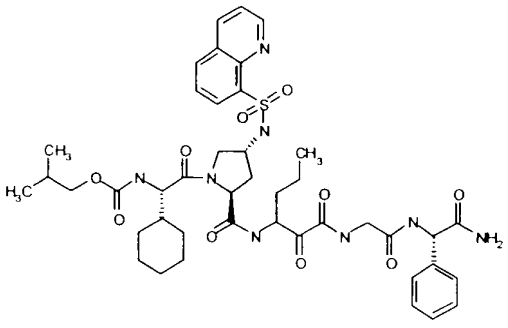

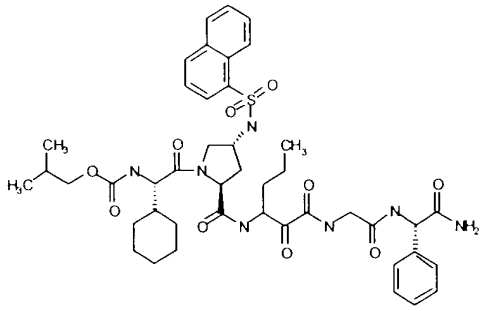

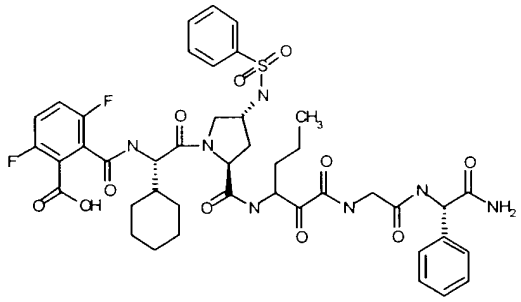

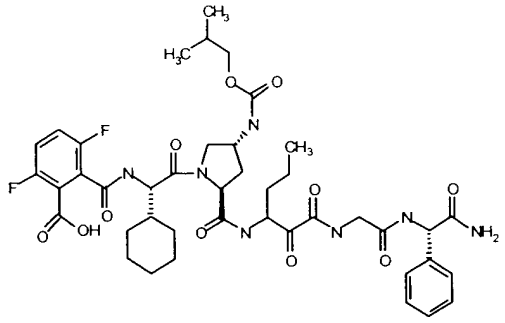

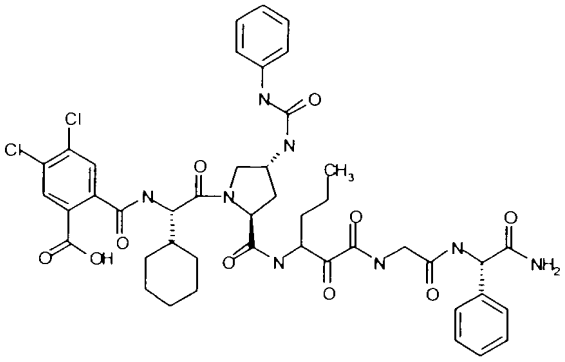

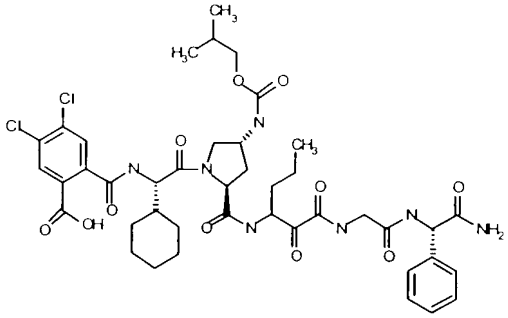

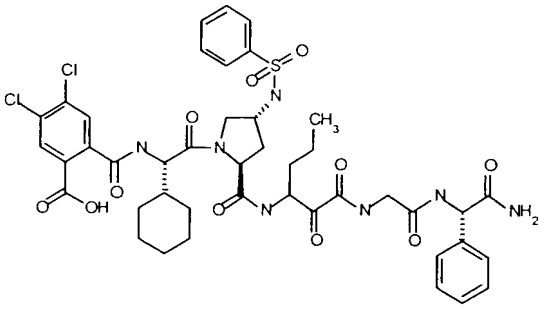

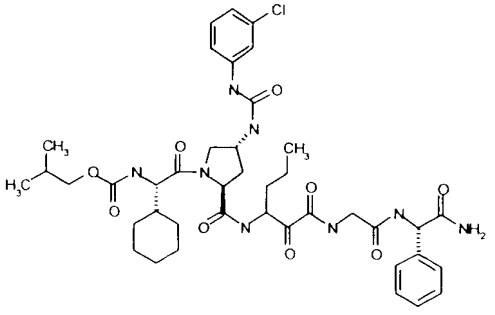

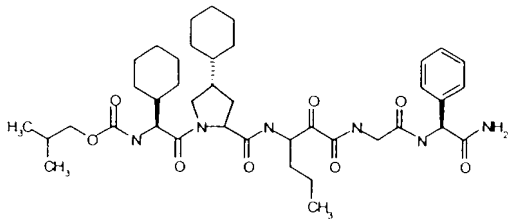

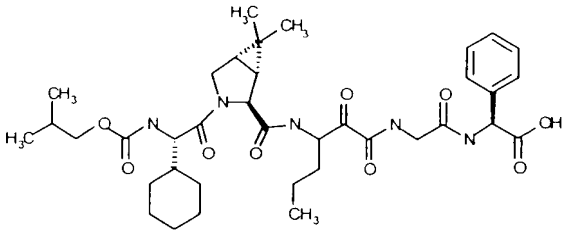

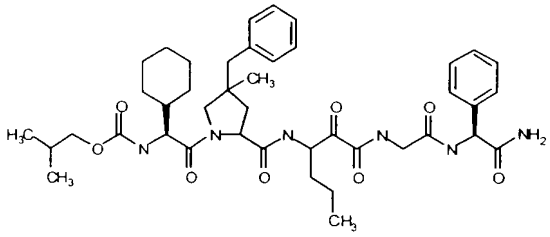

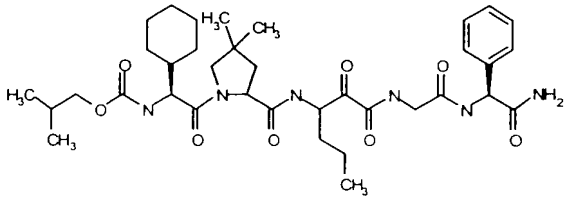

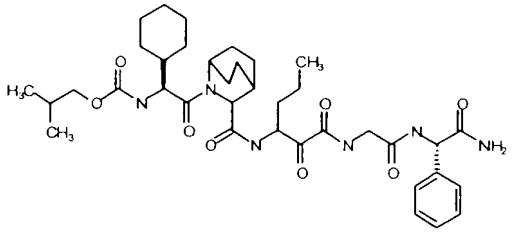

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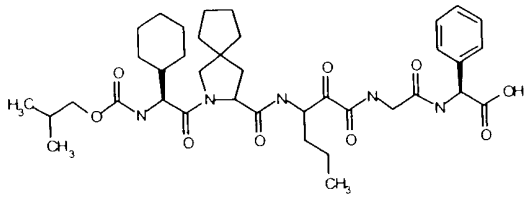

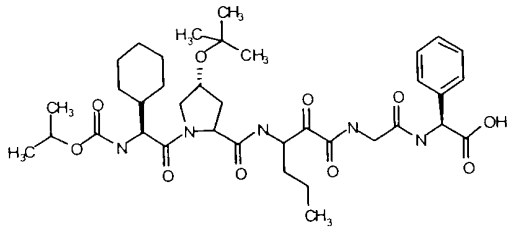

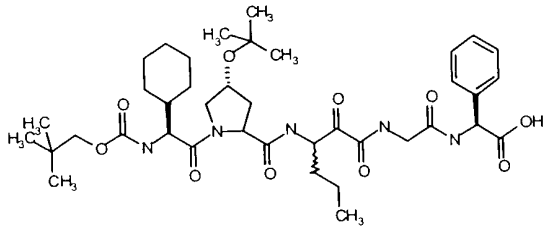

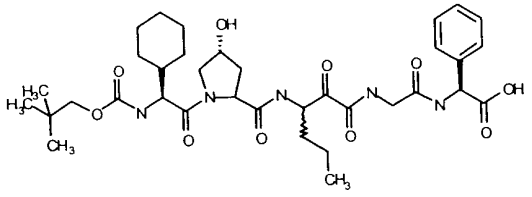

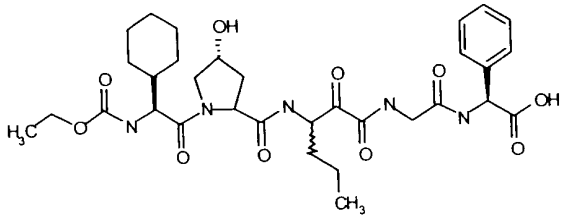

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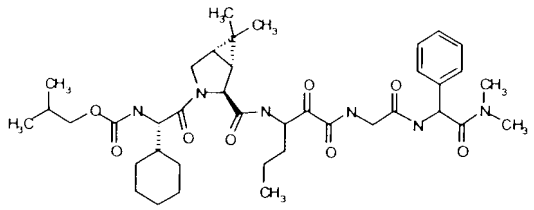

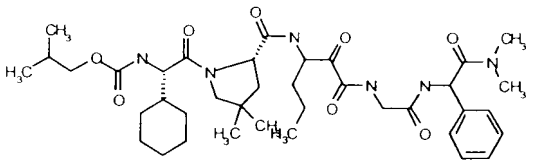

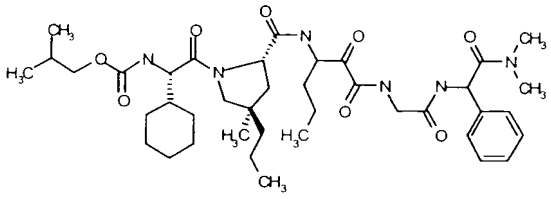

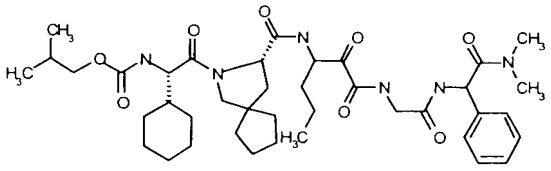

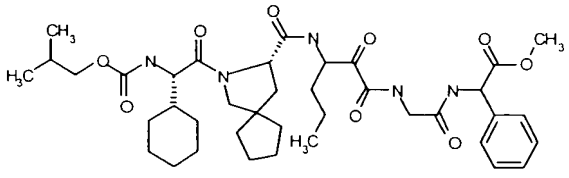

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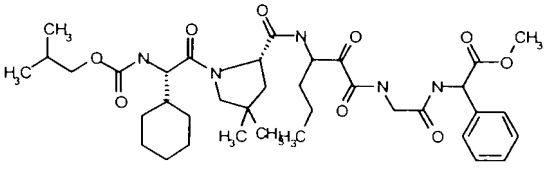

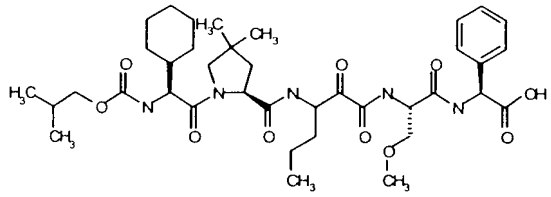

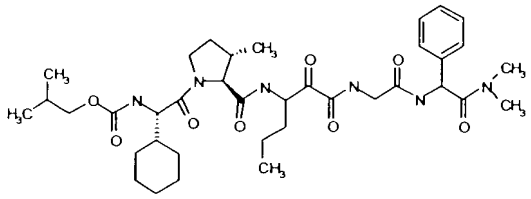

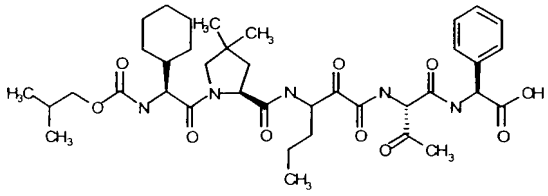

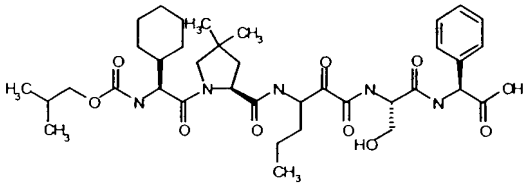

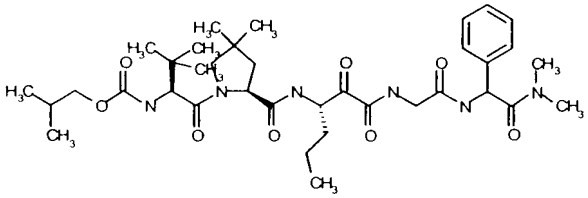

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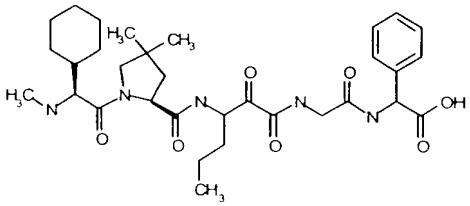

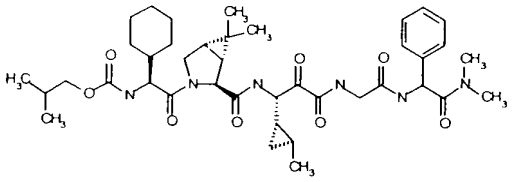

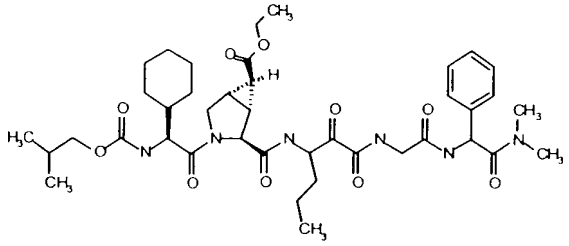

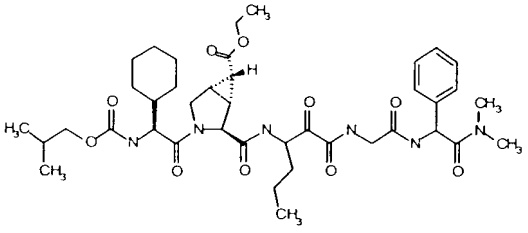

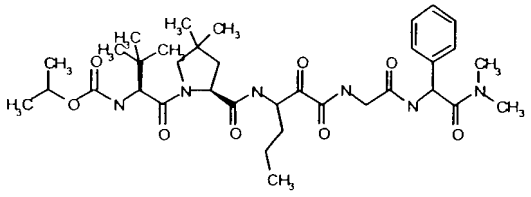

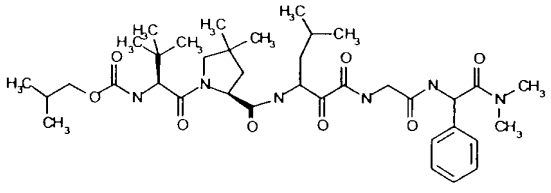

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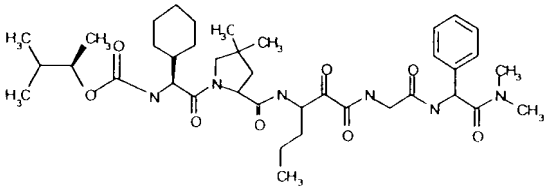

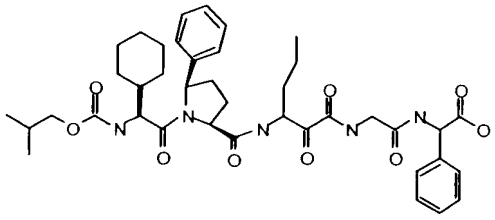

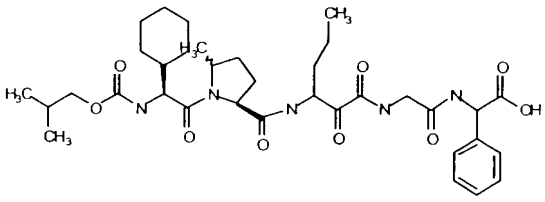

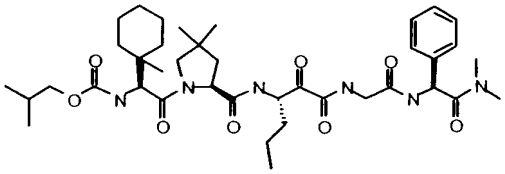

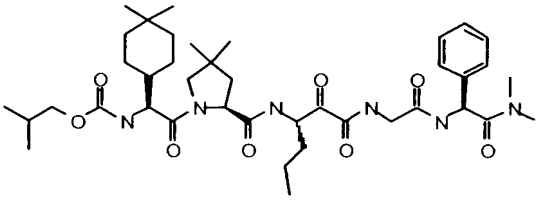

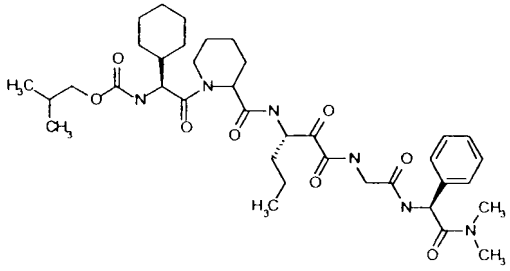

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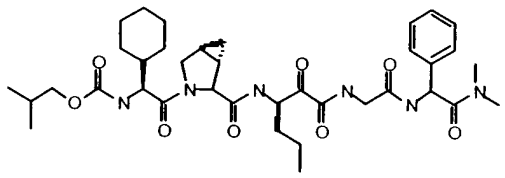

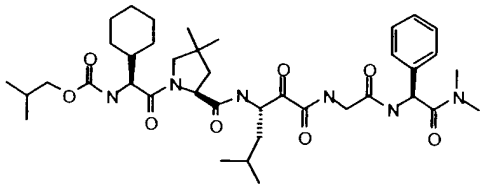

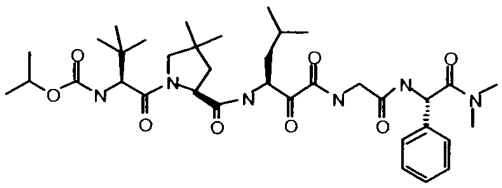

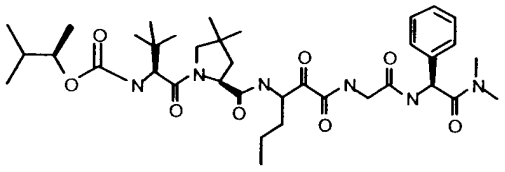

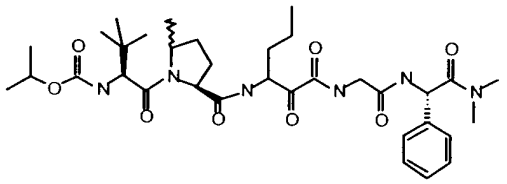

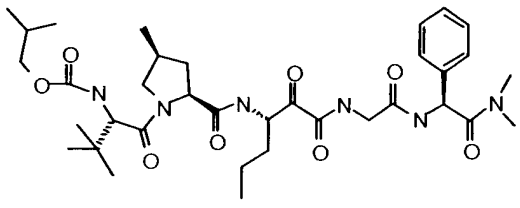

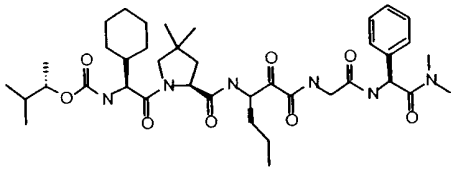

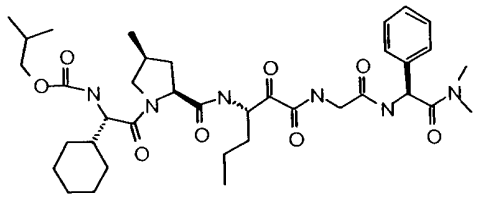

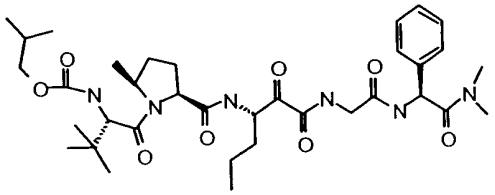

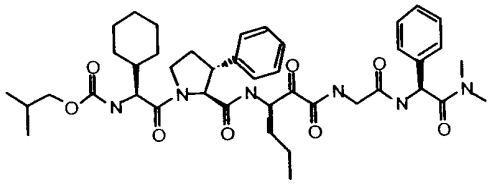

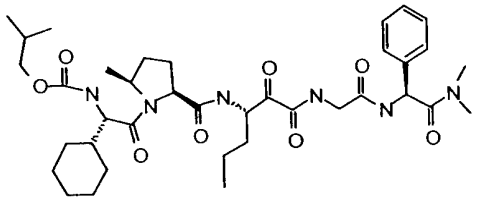

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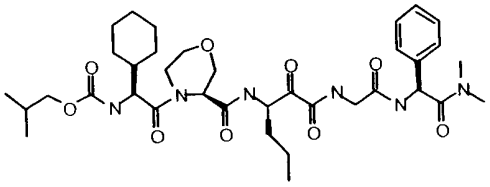

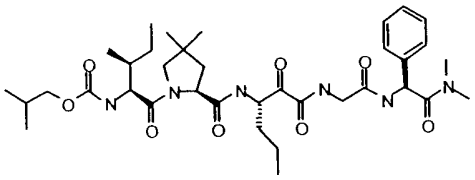

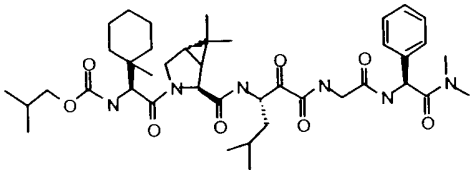

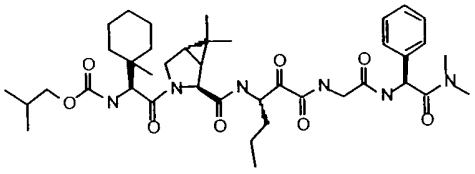

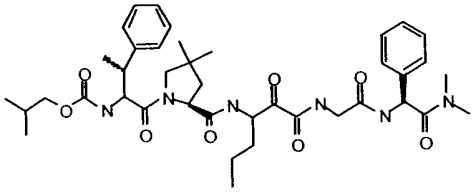

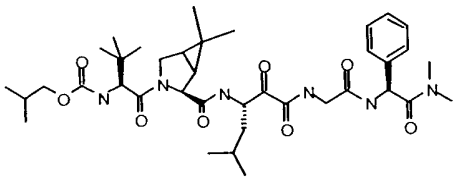

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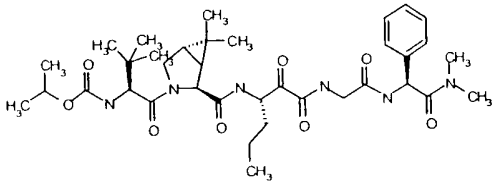

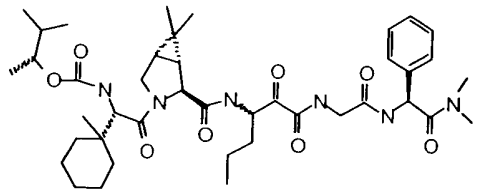

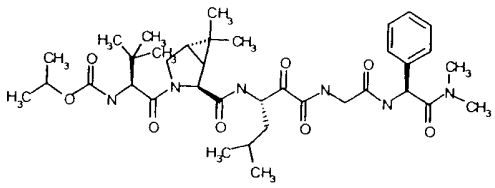

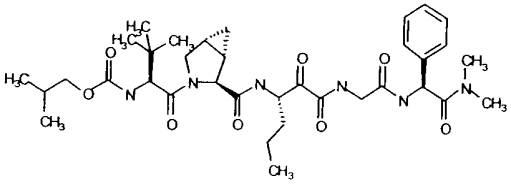

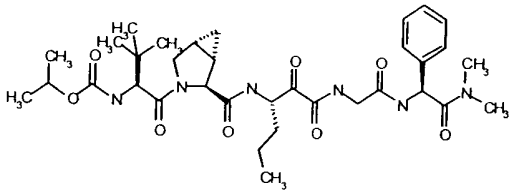

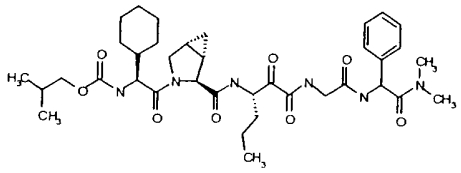

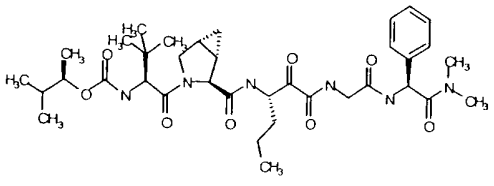

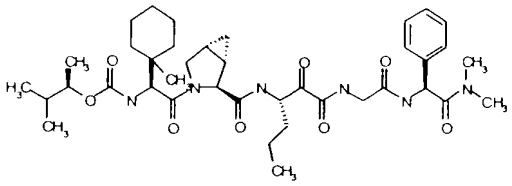

Depending upon their structure, the compounds of the invention may form pharmaceutically acceptable salts with organic or inorganic acids, or organic or inorganic bases. Examples of suitable acids for such salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those skilled in the art. For formation of salts with bases, suitable bases are, for example, NaOH, KOH, NH_4OH, tetraalkylammonium hydroxide, and the like.

In another embodiment, this invention provides pharmaceutical compositions comprising the inventive peptides as an active ingredient. The pharmaceutical compositions generally additionally comprise a pharmaceutically acceptable carrier diluent, excipient or carrier (collectively referred to herein as carrier materials). Because of their HCV inhibitory activity, such pharmaceutical compositions possess utility in treating hepatitis C and related disorders.

In yet another embodiment, the present invention discloses methods for preparing pharmaceutical compositions comprising the inventive compounds as an active ingredient. In the pharmaceutical compositions and methods of the present invention, the active ingredients will typically be administered in admixture with suitable carrier materials suitably selected with respect to the intended form of administration, i.e. oral tablets, capsules (either solid-filled, semi-solid filled or liquid filled), powders for constitution, oral gels, elixirs, dispersible granules, syrups, suspensions, and the like, and consistent with conventional pharmaceutical practices. For example, for oral administration in the form of tablets or capsules, the active drug component may be combined with any oral non-toxic pharmaceutically acceptable inert carrier, such as lactose, starch, sucrose, cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate,

talc, mannitol, ethyl alcohol (liquid forms) and the like. Moreover, when desired or needed, suitable binders, lubricants, disintegrating agents and coloring agents may also be incorporated in the mixture. Powders and tablets may be comprised of from about 5 to about 95 percent inventive composition. Suitable binders include starch, gelatin, natural sugars, corn sweeteners, natural and synthetic gums such as acacia, sodium alginate, carboxymethylcellulose, polyethylene glycol and waxes. Among the lubricants there may be mentioned for use in these dosage forms, boric acid, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrants include starch, methylcellulose, guar gum and the like.

Sweetening and flavoring agents and preservatives may also be included where appropriate. Some of the terms noted above, namely disintegrants, diluents, lubricants, binders and the like, are discussed in more detail below.

Additionally, the compositions of the present invention may be formulated in sustained release form to provide the rate controlled release of any one or more of the components or active ingredients to optimize the therapeutic effects, i.e. HCV inhibitory activity and the like. Suitable dosage forms for sustained release include layered tablets containing layers of varying disintegration rates or controlled release polymeric matrices impregnated with the active components and shaped in tablet form or capsules containing such impregnated or encapsulated porous polymeric matrices.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injections or addition of sweeteners and pacifiers for oral solutions, suspensions and emulsions. Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier such as inert compressed gas, e.g. nitrogen.

For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides such as cocoa butter is first melted, and the active ingredient is

dispersed homogeneously therein by stirring or similar mixing. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby solidify.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable transdermally. The transdermal compositions may take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

Preferably the compound is administered orally, intravenously or subcutaneously.

Preferably, the pharmaceutical preparation is in a unit dosage form. In such form, the preparation is subdivided into suitably sized unit doses containing appropriate quantities of the active components, e.g., an effective amount to achieve the desired purpose.

The quantity of the inventive active composition in a unit dose of preparation may be generally varied or adjusted from about 1.0 milligram to about 1,000 milligrams, preferably from about 1.0 to about 950 milligrams, more preferably from about 1.0 to about 500 milligrams, and typically from about 1 to about 250 milligrams, according to the particular application. The actual dosage employed may be varied depending upon the patient's age, sex, weight and severity of the condition being treated. Such techniques are well known to those skilled in the art.

Generally, the human oral dosage form containing the active ingredients can be administered 1 or 2 times per day. The amount and frequency of the administration will be regulated according to the judgment of the attending clinician. A generally recommended daily dosage regimen for oral administration

may range from about 1.0 milligram to about 1,000 milligrams per day, in single or divided doses.

Some useful terms are described below:

Capsule - refers to a special container or enclosure made of methyl cellulose, polyvinyl alcohols, or denatured gelatins or starch for holding or containing compositions comprising the active ingredients. Hard shell capsules are typically made of blends of relatively high gel strength bone and pork skin gelatins. The capsule itself may contain small amounts of dyes, opaquing agents, plasticizers and preservatives.

Tablet- refers to a compressed or molded solid dosage form containing the active ingredients with suitable diluents. The tablet can be prepared by compression of mixtures or granulations obtained by wet granulation, dry granulation or by compaction.

Oral gel- refers to the active ingredients dispersed or solubilized in a hydrophillic semi-solid matrix.

Powder for constitution refers to powder blends containing the active ingredients and suitable diluents which can be suspended in water or juices.

Diluent - refers to substances that usually make up the major portion of the composition or dosage form. Suitable diluents include sugars such as lactose, sucrose, mannitol and sorbitol; starches derived from wheat, corn, rice and potato; and celluloses such as microcrystalline cellulose. The amount of diluent in the composition can range from about 10 to about 90% by weight of the total composition, preferably from about 25 to about 75%, more preferably from about 30 to about 60% by weight, even more preferably from about 12 to about 60%.

Disintegrant - refers to materials added to the composition to help it break apart (disintegrate) and release the medicaments. Suitable disintegrants include starches; "cold water soluble" modified starches such as sodium carboxymethyl starch; natural and synthetic gums such as locust bean, karaya, guar, tragacanth and agar; cellulose derivatives such as methylcellulose and sodium carboxymethylcellulose; microcrystalline celluloses and cross-linked

microcrystalline celluloses such as sodium croscarmellose; alginates such as alginic acid and sodium alginate; clays such as bentonites; and effervescent mixtures. The amount of disintegrant in the composition can range from about 2 to about 15% by weight of the composition, more preferably from about 4 to about 10% by weight.

Binder - refers to substances that bind or "glue" powders together and make them cohesive by forming granules, thus serving as the "adhesive" in the formulation. Binders add cohesive strength already available in the diluent or bulking agent. Suitable binders include sugars such as sucrose; starches derived from wheat, corn rice and potato; natural gums such as acacia, gelatin and tragacanth; derivatives of seaweed such as alginic acid, sodium alginate and ammonium calcium alginate; cellulosic materials such as methylcellulose and sodium carboxymethylcellulose and hydroxypropylmethylcellulose; polyvinylpyrrolidone; and inorganics such as magnesium aluminum silicate. The amount of binder in the composition can range from about 2 to about 20% by weight of the composition, more preferably from about 3 to about 10% by weight, even more preferably from about 3 to about 6% by weight.

Lubricant - refers to a substance added to the dosage form to enable the tablet, granules, etc. after it has been compressed, to release from the mold or die by reducing friction or wear. Suitable lubricants include metallic stearates such as magnesium stearate, calcium stearate or potassium stearate; stearic acid; high melting point waxes; and water soluble lubricants such as sodium chloride, sodium benzoate, sodium acetate, sodium oleate, polyethylene glycols and d'l-leucine. Lubricants are usually added at the very last step before compression, since they must be present on the surfaces of the granules and in between them and the parts of the tablet press. The amount of lubricant in the composition can range from about 0.2 to about 5% by weight of the composition, preferably from about 0.5 to about 2%, more preferably from about 0.3 to about 1.5% by weight.

Glident - material that prevents caking and improve the flow characteristics of granulations, so that flow is smooth and uniform. Suitable glidents include

silicon dioxide and talc. The amount of glident in the composition can range from about 0.1% to about 5% by weight of the total composition, preferably from about 0.5 to about 2% by weight.

Coloring agents - excipients that provide coloration to the composition or the dosage form. Such excipients can include food grade dyes and food grade dyes adsorbed onto a suitable adsorbent such as clay or aluminum oxide. The amount of the coloring agent can vary from about 0.1 to about 5% by weight of the composition, preferably from about 0.1 to about 1%.

Bioavailability - refers to the rate and extent to which the active drug ingredient or therapeutic moiety is absorbed into the systemic circulation from an administered dosage form as compared to a standard or control.

Conventional methods for preparing tablets are known. Such methods include dry methods such as direct compression and compression of granulation produced by compaction, or wet methods or other special procedures. Conventional methods for making other forms for administration such as, for example, capsules, suppositories and the like are also well known.

Another embodiment of the invention discloses the use of the pharmaceutical compositions disclosed above for treatment of diseases such as, for example, hepatitis C and the like. The method comprises administering a therapeutically effective amount of the inventive pharmaceutical composition to a patient having such a disease or diseases and in need of such a treatment.

In yet another embodiment, the compounds of the invention may be used for the treatment of HCV in humans in monotherapy mode or in a combination therapy (e.g., dual combination, triple combination etc.) mode such as, for example, in combination with antiviral and/or immunomodulatory agents. Examples of such antiviral and/or immunomodulatory agents include Ribavirin (from Schering-Plough Corporation, Madison, New Jersey) and Levovirin™ (from ICN Pharmaceuticals, Costa Mesa, California), VP 50406™ (from Viropharma, Incorporated, Exton, Pennsylvania), ISIS 14803™ (from ISIS Pharmaceuticals, Carlsbad, California), Heptazyme™ (from Ribozyme Pharmaceuticals, Boulder,

Colorado), VX 497™ (from Vertex Pharmaceuticals, Cambridge, Massachusetts), Thymosin™ (from SciClone Pharmaceuticals, San Mateo, California), Maxamine™ (Maxim Pharmaceuticals, San Diego, California), mycophenolate mofetil (from Hoffman-LaRoche, Nutley, New Jersey), interferon (such as, for example, interferon-alpha, PEG-interferon alpha conjugates) and the like. "PEG-interferon alpha conjugates" are interferon alpha molecules covalently attached to a PEG molecule. Illustrative PEG-interferon alpha conjugates include interferon alpha-2a (Roferon™, from Hoffman La-Roche, Nutley, New Jersey) in the form of pegylated interferon alpha-2a (e.g., as sold under the trade name Pegasys™), interferon alpha-2b (Intron™, from Schering-Plough Corporation) in the form of pegylated interferon alpha-2b (e.g., as sold under the trade name PEG-Intron™), interferon alpha-2c (Berofor Alpha™, from Boehringer Ingelheim, Ingelheim, Germany) or consensus interferon as defined by determination of a consensus sequence of naturally occurring interferon alphas (Infergen™, from Amgen, Thousand Oaks, California).

As stated earlier, the invention includes tautomers, rotamers, enantiomers and other stereoisomers of the inventive compounds also. Thus, as one skilled in the art appreciates, some of the inventive compounds may exist in suitable isomeric forms. Such variations are contemplated to be within the scope of the invention.

Another embodiment of the invention discloses a method of making the compounds disclosed herein. The compounds may be prepared by several techniques known in the art. Representative illustrative procedures are outlined in the following reaction schemes. It is to be understood that while the following illustrative schemes describe the preparation of a few representative inventive compounds, suitable substitution of any of both the natural and unnatural amino acids will result in the formation of the desired compounds based on such substitution. Such variations are contemplated to be within the scope of the invention.

Abbreviations which are used in the descriptions of the schemes, preparations and the examples that follow are:

THF: Tetrahydrofuran

DMF: *N*,*N*-Dimethylformamide

EtOAc: Ethyl acetate

AcOH: Acetic acid

HOOBt: 3-Hydroxy-1,2,3-benzotriazin-4(3*H*)-one

EDCI: 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride

NMM: *N*-Methylmorpholine

ADDP: 1,1'-(Azodicarbobyl)dipiperidine

DEAD: Diethylazodicarboxylate

MeOH: Methanol

EtOH: Ethanol

Et_2O: Diethyl ether

DMSO: Dimethylsulfoxide

HOBt: N-Hydroxybenzotriazole

PyBrOP: Bromo-*tris*-pyrrolidinophosphonium hexafluorophosphate

DCM: Dichloromethane

DCC: 1,3-Dicyclohexylcarbodiimide

TEMPO: 2,2,6,6-Tetramethyl-1-piperidinyloxy

Phg: Phenylglycine

Chg: Cyclohexylglycine

Bn: Benzyl

Bzl: Benzyl

Et: Ethyl

Ph: Phenyl

iBoc: isobutoxycarbonyl

iPr: isopropyl

^tBu or Bu^t: *tert*-Butyl

Boc: tert-Butyloxycarbonyl